FEVER IN RENAL TRANSPLANT RECIPIENTS – AN INQUIRY INTO ETIOLOGY

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CERTIFICATE

This is to certify that this dissertation titled **"FEVER IN RENAL TRANSPLANT RECIPIENTS - AN INQUIRY INTO ETIOLOGY"** is the bonafide work done by **Dr. JAGDISH K.,** Post Graduate Student (2010 – 2013) in the Department of General Medicine, Govt. Stanley Medical College and Hospital, Chennai under the direct guidance and supervision and in partial fulfillment of the regulations laid down by The Tamil Nadu Dr. M.G.R. Medical University, Chennai for M.D. Branch I, General Medicine Degree Examination to be held in April 2013.

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DECLARATION

I, **Dr. JAGDISH K.,**solemnly declare that the dissertation titled **"FEVER IN RENAL TRANSPLANT RECIPIENTS - AN INQUIRY INTO ETIOLOGY"** is a bonafide work done by me at Govt. Stanley Medical College and Hospital from MAR 2012 to NOV 2012 under the guidance and supervision of my unit chief,

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Dr. Jagdish K

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LIST OF ABBREVIATIONS

PGE2	Prostaglandin E2
TLR	Toll Like Receptor
TSST	Toxic Shock Syndrome Toxin
MHC	Major Histocompatibility Complex
TNF	Tumor Necrosis Factor
CNTF	CiliaryNeurotrophic Factor
IFN	Interferon
IL	Interleukin
c-AMP	Cyclic Adenosine Mono Phosphate
CD	Cluster Differentiation
HLA	Human Leucocyte Antigen
MMF	Mycofenolate Mofetil
mTOR	Mammalian Target of Rapamycin
BOOP	Bronchiolitis Obliterating Organising Pneumonia
PTLD	Post Transplant LymphoproliferativeDIsorder
FUO	Fever of Unknown Origin
NODAT	New Onset Diabetes After Transplant
CT	Computerised Tomography
PCR	Polymerase Chain Reaction
UTI	Urinary Tract Infection

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INTRODUCTION

Fever is always a mysterious and interesting puzzle to solve. Despite interests in fever in competent host, most fever go undiagnosed (even without consulting a physician). Fortunately,fever in these patients neither leaves traces, nor any damage in the host.

Fever, in a compromised host, is always undisputedly significant as their ability to mount inflammation/immunity is blunted and renal transplant recipient patients are no different. Chronic kidney disease, by itself, is an immunocompromised state. To significantly add to that, these patients will be humungously immunosuppressed. Unlike others,fever in compromised host is a medical emergency.

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INTRODUCTION

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A prevalence of different etiology manifesting as fever is of utmost importance, as it gives you the most common causes in our locality, which might or might not be the same as that of a western literature/ a study done elsewhere in the country. It is very likely that there will be difference in the fever pattern between different study population[21]

It helps us to get early diagnosis, knowing the disease pattern and to start empirical drugs against the disease that is prevalent, which saves time, money and more importantly “the precious life” of renal transplant recipient patients, who mean even more to his family, after transplant. Such is the impact.

REVIEW OF LITERATURE

INTRODUCTION

Fever is an interesting companion of mankind from age old times. Whether it is a friend or foe, is always an interesting question. It is actually defined as an elevation in core body temperature above the daily range for an individual. It is essential to describe a normal body temperature.

NORMAL BODY TEMPERATURE

It varies throughout the course of the day with maximum normal oral temperature at 6 AM is 37.2 ºC (98.9 ºF) and the maximum level at 4 PM is 37.7 ºC (99.9 ºF), both values defining the 99th percentile for healthy subjects. It is controlled in anterior hypothalamus with predominant site of production being muscle and liver, whereas predominant site of dissipation is skin and lungs. Unfortunately due to extremes of temperature, it is often not possible to maintain temperature homeostasis with the help of dress and shelter[1].

The maximum normal oral temperature at 6 AM is 37.2 ºC (98.9 ºF) and the maximum level at 4 PM is 37.7 ºC (99.9 ºF) both values defining the 99th percentile for healthy subjects. So a morning reading of >37.2 ºC (98.9 ºF) or an afternoon temperature of >37.7 ºC (99.9 ºF) would be considered a fever. Rectal temperature is0.6 ºC (1.0 ºF) higher than oral readings. Oral readings are low probably because of mouth breathing, whereas lower esophageal temperature reflects the core body temperature and tympanic membrane temperature is close to it.

Normal daily variation in temperature is usually between 0.5 – 1 degree Celsius. Range changes in pathological states.

Menstruation, ovulation, pregnancy, postprandial states can have variation, contrary to routine rule. Children have a fixed daily variation, whereas elderly weakly mount fever[2].

FEVER, HYPERTHERMIA, AND HYPERPYREXIA

Fever, hyperthermia, and hyperpyrexia are not synonymous terms.

Fever:

Fever thermostat is located in hypothalamus, which decides the body temperature. An upward shift in the set point happens in fever, mediated by PGE2. Once the hypothalamic set-point is raised, this activates neurons in the vasomotor center to commence vasoconstriction and increase heat production in the periphery.

Heat conservation by vasoconstriction will raise core body temperature 1ºC. Non shivering thermo genesis due to uncoupling of oxidative phosphorylation takes place in muscle and adipose tissue.

Heat conservation and thermogenesis account for the major source of heat generation, associated with a marginal heat production in liver. Shivering of muscle is usually not needed unless there is a rapid rise in set point. Human lifestyle changes accounts for remaining need.

When the set point is reset, opposite happens, resulting in vasodilatation and sweating.

Hyperthermia:

In contrast to fever, thermoregulatory set point remains at normothermic levels and temperature increases and overwhelms the ability to lose heat, resulting in alarmingly high body temperature

Hyperpyrexia:

Hyperpyrexia is alarmingly high temperature of >41.5 ºC, which is observed usually in central nervous system hemorrhages and infections.

A pyrogen is any substance that can trigger fever and it can be either exogenous or endogenous. Exogenous pyrogens are endotoxins of gram negative infections and exotoxins and enterotoxins of gram positive infections. Endotoxins, besides fever, are responsible for various other pathogenetic process[3]. Endotoxins are toll-like receptor (TLR) ligands, that activates macrophage, to generate cytokines resulting in fever[4]

The toxic shock syndrome toxin (TSST-1) of Staphylococcus aureus isolated and other enterotoxins from S. aureus and exotoxins from group A streptococcus act both as direct toxins and serve as "superantigens" [5,6]. Superantigen interacts with major histocompatibility complex (MHC) II and a number of T cell subsets[7,8] to release pyrogenic cytokines

Pyrogenic cytokines

Pyrogenic cytokines are proteins that regulate various components of immune system. Few important ones are namely IL-1, IL-6, tumor necrosis factor (TNF) and Ciliary Neurotrophic Factor (CNTF), Interferon (IFN)-α. Others likely exist.

Inflammation, trauma or immune complex can also induce these proteins.

ELEVATION OF THE HYPOTHALAMIC SET-POINT BY CYTOKINES

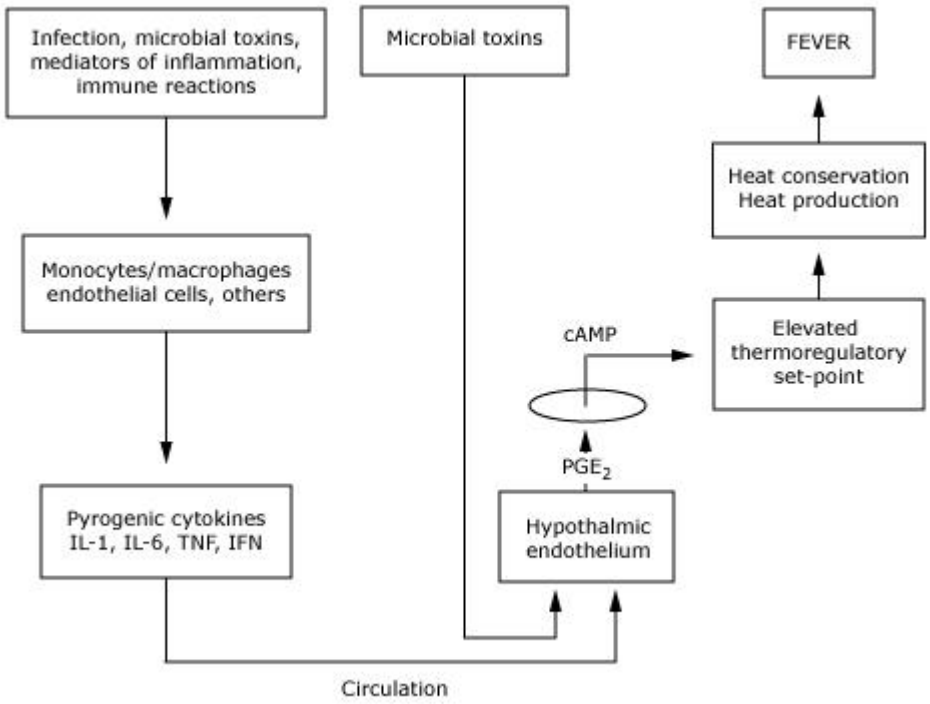


FIGURE 1: PATHWAYS OF FEVER PRODUCTION

Cytokines stimulate PGE2 both centrally and peripherally. Central production is responsible for fever, whereas the peripheral production is responsible for myalgia, arthralgia and other prodromes. PGE2 stimulate receptors on glial cells to activate CAMP, which resets set point to a higher level[10].

It is very evident that anti cytokine therapy can mask fever. Despite therapy, fever can manifest due to blocking of selective cytokines, while the other cytokines express. It can also manifest if production overwhelms therapy. Alternatively, microbial products can directly stimulate PGE2 in brain.

Patient, whose cytokines are inhibited by either congenital or acquired causes, can manifest fever, but the incidence and intensity is grossly low in comparison with a normal host.

FEVER IN COMPROMISED HOST

An immunocompromised host behave in a totally different way when compared to normal person in immune response, and in mounting immunity against infections[10].

FEVER, IMMUNOSUPPRESSION, AND INFECTION

Fever may be the only manifestation of life threatening infection in the compromised patient. No single pattern or degree of fever is diagnostic of an infectious or a non-infectious cause[11]. It can be muted in patients with an immunocompromised state, be it congenital or acquired[12]

Decision of immediate evaluation and prompt empirical treatment is of utmost importance in compromised host[13, 14]. Few of those life threatening conditions are profound neutropenia and splenectomy. It also depends on the etiology of neutropenia, duration and associated defences of the host.

Etiology of neutropenia is very important. Patients who develop neutropenia after viral infection do much better than immunosuppresed patient with drugs after post-transplant or cancer chemotherapy. If you look deeply the latter group also have mucosal breech due to inhibition of rapidly proliferating cells, in gastro intestinal tract, respiratory tract and urinary tract[15].

Functionally asplenic or who have had a splenectomy, have increased vulnerability fulminant infections with encapsulated organisms. Most common infection includes *Streptococcus pneumoniae, Neisseria*

meningitidis, and *Haemophilus influenza.* Incidence is very high if they are not immunized or in patients with emergency splenectomy. These subsets of patients are highly fragile because they go in for multi organ dysfunction and cardiovascular collapse very early in clinical course.

Besides neutropenia, life threatening infections are common in individuals with severe derangement of humoral and cell mediated immunity. Patients with CD4 cell counts less than 200 per cubic millimeter in children more than six years of age and adults are at risk for life-threatening infections with *Pneumocystis carinii* and other opportunistic infections, which will have a fulminant course, if not treated early. Except tuberculosis, opportunistic infection is uncommon if CD4 count is less than 200. Incidence of Mycobacterium avium-intracellulare is unlikely with CD4 count less than 50.

Patients, who are on immunosuppressive therapy after organ transplantation or for an autoimmune disease, are at a high risk of being infected with a gram positive or gram negative organisms during early days. Subsequently they succumb to organisms that are cleared by cell mediated immunity (Toxoplasma, Pneumocystis and so on)

INFECTIONS IN IMMUNOCOMPROMISED – A WIDE SPECTRUM

There is an endless list of infection in the immunocompromised host. It is possible that every organism existing can become invasive in these patients. No algorithm is appropriate in these individuals, but the organism can be predicted based on the degree, duration of immunosuppresion and the common organisms that is prevalent in the locality.

A change in trend has been observed over the past few decades in a variety of patients with different etiology.

One of the most important threats in a compromised host comes from bacteriae.

In neutropenics, in the developing nation, the most common isolates are gram negative organisms, namely Klebsiella, Pseudomonas, E coli.

Despite their abundance, infection with gram positive organism, is usually not life threatening. Patients with gram negative bugs can pursue a fulminant course, if not treated early and appropriately.

Individuals who underwent splenectomy or individuals harbouring HIV infection are prone to develop infections by capsulated organisms and gram negative bacteriae.

Patients with neutropenia due to cytotoxic therapy are susceptible to infections with viruses (herpes viruses and respiratory viruses), fungi and parasites.

For practical purposes, neutropenics are divided into low- and high-risk groups based on the projected duration of neutropenia. Low risk groups are those with projected duration of neutropenia less than 10 days and they fair well to come out of the crisis. High risk patients with duration lasting more than 10 days are vulnerable to acute bacterial infections, fungi, parasites and viruses. In addition, they are prone for recurrent infections, relapse, polymicrobial infections. Obviously, the latter situation poses a diagnostic as well as a therapeutic challenge.

Patients with hematological transplants, succumb to neutropenia early. Once reconstitution occurs, they are prone to infection with capsulated organisms. Those with solid organ transplantation, it depends on the type and nature and duration since transplant.

Gram negative infection and sepsis are common in renal transplant patients. Enterally derived pathogens and ascending cholangitis are common in liver transplant patients. Mediastinitis and pneumonia are more common in heart or lung transplantation.

Similar to bacteriae, viral infections are also predisposed by many factors. One such example is the timing of infection in herpes virus in marrow or solid organ transplantation, where different species of herpes virus present in different months.

Epstein Barr virus and its clinical features vary widely from a benign to completely malignant disease.

In solid organ transplantation with central nervous involvement, Listeria and Cryptococcus should always be kept in mind.

Other possible infections in HIV positive patients include a variety of agents depending on the CD4 count. Pneumocystis infection with CD4 counts less than 200. Mycobacterium avium-intracellulare with CD4 count less than 50 and mycobacterium tuberculosis can infect in a variety of CD4 count.

RENAL TRANSPLANT

Renal transplantation is the best available treatment at present for patients with chronic kidney disease. Around the globe the procedure has become rampant. When azathioprine and prednisone initially were used as immunosuppressive drugs in the 1960s, the results with properly matched familial donors were superior to those with organs from deceased donors; 75–90% compared with 50–60% graft survival rates at 1 year. Well today the one year survival rate for deceased donor is 89% and for living donor is 95%. Today the average survival time for a live matched donor is 20 years and for deceased donor is 14 years

Post-transplant mortality rate is highest in the first year and is age dependent, which is directly proportional to age. Non-compliance of drug may drastically worsen renal function through rejection. Most grafts, however, succumb at varying rates to a chronic process consisting of interstitial fibrosis, tubular atrophy, vasculopathy, and glomerulopathy, the pathogenesis of which is incompletely understood. There are 2,00,000 functioning kidneys after transplant around the world as it totally changes the lifestyle of the patient when compared to other modes of renal replacement therapy.

Expanded Criteria Donor (ECD)
1. Deceased donor >60 years 2. Deceased donor >50 years and hypertension and creatinine>1.5 g/dL 3. Deceased donor >50 years and hypertension and death caused by cerebrovascular accident (CVA) 4. Deceased donor >50 years and death caused by CVA and creatinine>1.5 mg/Dl
Donation after Cardiac Death (DCD)
1. Brought in dead 2. Unsuccessful resuscitation 3. Awaiting cardiac arrest 4. Cardiac arrest after brainstem death 5. Cardiac arrest in a hospital patient

TABLE 1: EXPANDED CRITERIA FOR DONOR AND DONATION AFTER CARDIAC DEATH

Recipient Selection

Very few absolute contraindications to renal transplantation exist. The procedure is relatively non-invasive, and the organ is placed in the inguinal fossa outside the peritoneum. Recipients can be discharged within a week of transplant, provided there are no perioperative complications.

Patient receiving transplant invariably have a morbidity and mortality benefit, as compared to those on long term dialysis. Elderly and older patients, even if they have a higher mortality, do much better with transplant than dialysis. This resulted in substantial demand to the deceased kidneys as the need keeps on multiplying rapidly. This poses a threat to the policy makers to use stringent guidelines for the recipients.

Recommendation is a minimum life expectancy should be more than 5 years.

It applies to both deceased and living donor transplantation and this is due to the high immediate transplant period complications, which is very high when compared to those on dialysis. Risk benefit ratio has to be thoroughly analysed. Patients should be thoroughly screened for HIV and hepatitis before considering transplant. Most places consider this as near

absolute contraindication for transplant. But people do operate in few centers, to find out the superiority of one over the other.

Immunological absolute contraindication includes the presence of pre-existing antibody that is going to reject the kidneys immediately. They are anti ABO antibody and anti HLA antibody against the organ. All necessary steps to overcome such mismatch, should be done.

Donor Selections

Donors can be deceased or volunteer living donors. The living donors are selected from the family to have more HLA match. Living volunteer donors should have the same ABO blood group and should be normal on physical examination. However we can transplant a kidney from O blood group donor to a recipient of any blood group. Renal arteriography should be done to find out stenosis, variations and other abnormalities of the vessel, which can affect the procedure and can delay the ischemic time. Donors are increasingly operated laprascopically these days, which has reduced the hospital stay, scar, and nosocomial infection. Deceased donors should be free of malignant neoplastic disease, hepatitis, and HIV because of possible transmission to the recipient. Graft failure increase when the donor is aged or has a pre-existing renal dysfunction or prolonged period of ischemia and storage.

Tissue Typing and Clinical Immunogenetics:

HLA major histocompatability matching is an extremely important criterion for renal allograft, donor selection. Each individual has a single region that is located in the sixth chromosome which encodes major transplantation antigen.

HLA antigens DNA genomic sequences are increasingly being used these days. Blood group antigens, endothelial antigens and minor antigens play an important role. Few of the HLA identical grafts are also rejected. All these tell us they are sensitized to minor antigens previously. Well these antigens are relatively suppressible by drugs provided no priming has occurred.

Immunosuppression:

The idea of increasing life span by organ transplantation had long been a dream for the medical fraternity. Early efforts at transplantation were unsuccessful due to inadequacies in surgical technique and insufficient knowledge of the immune system.

Many surgical procedures failed during the early days. This dated back to 1933.Total body irradiation was used as a tool to immunosuppress the patient in the early days, when the concept of

rejection was blossoming. Next came the era of steroids alone, which was not successful.

Subsequently, with the development of 6-mercaptopurine, azathioprine in the early 1960s, pharmacological suppression stole the show and has become the standard of care.

The first successful series of transplant were between 1962 and 1964. Sooner, the combination of azathioprine and steroids came to practice and was the widely used combination and became a routine pillar of immunosuppression.

As our knowledge of the immune system evolved with time, therapy targeted to specific immune-regulatory sites unfolded and raised new horizons in the treatment of transplant medicine. The first polyclonal antilymphocyte globulin was used in 1967 and it seeded the hopes and paved the way for other drugs.

Cyclosporine was introduced as a calcineurin inhibitor in 1980 and was combined with steroids, azathioprine, which created wonders in graft survival.

Both tacrolimus and mycophenolate mofetil were introduced in 1994. Tacrolimus has slowly replaced cyclosporine. MMF has virtually

replaced azathioprine universally. To expand the armamentarium further, sirolimus, a macrolide antibiotic, was introduced recently and the exact role of which is yet to be defined.

Then came the era when people started thinking about the side effects of the drugs which might affect the patients adversely and in turn can have a worse outcome in the graft.

BRIEF REVIEW OF THE INDIVIDUAL DRUGS:

Azathioprine:

It is a derivative of 6-mercaptopurine. It is used as an antimetabolite to decrease DNA and RNA synthesis and it is used as a drug for maintenance immunosuppression.

Toxicity:

- Marrow bi to tri lineage suppression
- Gastrointestinal symptoms
- Variable liver involvement
- Cholestasis
- Hair loss

Watchful monitoring of liver enzymes, pancreatic enzymes and complete blood count has to be done periodically.

Corticosteroids:

Corticosteroids inhibit production of IL –1 and IL-6 by macrophages. It also inhibits all stages of T-cell activation. It can be used as an induction agent, maintenance agent, and also useful in the treatment of acute rejection.

Toxicity:

- Cushings syndrome
- Osteopenia and easily prone for fracture
- Cataracts
- Impaired glucose intolerance
- Recurrent infections
- Dyslipidemia
- Poor wound healing
- Growth retardation

Cyclosporine:

It prevents the production of IL-2 and thus preventing the activation of helper T cells. It binds to cyclophilin binding protein and is used for induction as well as maintenance.

Toxicity:

- Nephrotoxicity
- Electrolyte imbalance commonly Hyperkalemia, hypomagnesemia
- Gastro intestinal intolerance
- Hypertrichosis, hirsuitism
- Gingival hyperplasia
- Dyslipidemia, glucose intolerance
- More prone for infection, malignancy, and hyperuricemia.

Switching from cyclosporine to tacrolimus alleviates side effects like hirsuitism.

Tacrolimus:

It is a macrolide antibiotic that inhibits the production of IL-2 by binding to tacrolimus binding protein. It is used as a maintenance therapy or it can be used in patients with refractory rejection.

Adverse effects

- Nephrotoxicity
- Neurotoxicity
- Glucose intolerance
- QT prolongation

Cosmetically, it is much superior to cyclosporine. It can cause reversible alopecia that can recover with lowering or stoppage of drugs.

Mycophenolate mofetil:

It is an inosine monophosphate dehydrogenase inhibitor and hence selectively impairs proliferation of B and T cells, without affecting the other rapidly proliferating cells due to rescue through salvage pathway. It is used for maintenance and chronic rejection. Newer enteric coated tablets have come to the market with decreased side effects.

Adverse effects:

- Gastro intestinal intolerance
- Pancytopenia

Hematological toxicity is worsened if concurrently administered with azathioprine.

Levels of the drug will be increased if concurrently administered with tacrolimus.

Sirolimus:

It acts by binding to FK binding protein, and it acts through mTOR(mammalian target of rapamycin). It inhibits cell proliferation by inhibiting G1 to S phase of cell cycle proliferation. This agent is used for maintenance immunosuppression and chronic rejection.

Adverse effects

- Electrolyte imbalance commonly potassium and magnesium disturbances
- Dyslipidemia
- Bicytopenia and occasionally tri lineage suppression
- Impaired wound healing
- Seroma

It has a relatively long half -life and hence it can have interactions with the other drugs. Despite that, it can be used with other drugs.

BIOLOGICAL AGENTS:

Polyclonal Antibodies:

Polyclonal antibodies are produced by injecting human lymphocyte into other species. It elicits an antibody response to human antibody. These antibodies are isolated and harvested. These antibodies kill the host lymphocytes by complement mediated lysis and by the activation of reticulo endothelial system.

Adverse effects:

- Fever, chills
- Pancytopenia
- Hemolyticanemia
- Respiratory distress
- Serum sickness and anaphylaxis

A major drawback is its association with non hodgkins lymphoma, when administered in high doses. [18]

MONOCLONAL ANTIBODIES:

Muromonab-CD3:

Muromonab-CD3 (OKT3) is a monoclonal antibody of immunoglobulin to the CD3 portion of the T-cell receptor and hence blocks the cell lineage activation. It is used for acute rejection and resistant cases.

Adverse effects

- Cytokine release syndrome
- Pulmonary edema

Monoclonal Anti-CD25 antibody:

Basiliximab and daclizumab are humanized monoclonal antibodies, which targets against IL-2 receptor. Both of them are used as induction agents, and are very similar in most aspects.

Adverse effects

- φ Hypersensitvity effects

Monoclonal Anti-CD20 antibody:

Rituximab is a monoclonal antibody that is directed against CD 20 of B cells. Its use is currently being studied in treatment of some forms of antibody-mediated rejection. Another area of possible utility is in the hypersensitized patient awaiting transplant. Monoclonal antibodies are relatively much expensive drugs when compared to their counterparts.

INFECTIONS IN POST RENAL TRANSPLANT:

Risk of infection in the post-transplant patient is determined by the extent of epidemiologic exposures and immune defects. Infection can be acquired from the organ, hospital or from the community. Sometimes the infection may get reactivated in the recipient, which was latent prior to immunosuppression. When there is a major infection the risk of mortality doubles and has huge impact in patients and graft survival.[20]

The precise timing of infection is determined by the interplay of host, environmental factors and the duration and degree of immunosuppression.

Timeline classification of renal transplant infection is broadly divided into three categories

1. Less than one month of transplant (perioperative and in-hospital infection)
2. Within one to six months of transplant
3. More than six months of transplant(some classify > one year)

INFECTION LESS THAN ONE MONTH:

In the first category which is basically early transplant infection, the source of infection either pre-exists in the host or acquired during the perioperative hospital stay. One common mode is the recipient is having a nidus of infection commonly a preoperative pneumonia or indwelling device related infection or infection of the fistula .

Most of the infection during this period is hospital acquired and can be either due to infections in the donor or transmitted through graft during different time. A notable difference is such infections through the graft need not follow the routine time table and can be early as well.

The most common infection at this point in time is similar to a normal person and is usually procedure related. Sterile techniques and meticulous hands yield excellent results. The routine nosocomial pathogens and sites are implicated in these patients. A good post-operative care invariably reduces the chances of infection widely. Apart from routine prophylaxis, an additional MRSA cover is all that is required.

A striking fact is opportunistic infection is uncommon in the first one month despite a heavy immune suppression in this period.

Bacterial and/or fungal organisms are transmitted by a contaminated allograft although donors are usually carefully screened for presence of contaminating organisms.

The categorization of post-transplant infections may be used in a variety of ways:

1. To shortlist infections in that stipulated period
2. As a clue to the presence of an excessive environmental hazard for the individual, either within the hospital or in the community, and
3. As a clue to the empirical treatment.

An infection that does not follow the timetable tells either the excessive vulnerability of the individual or excessive prevalence of infection in that particular community.

Prophylaxis of infection is usually based on the time table or the timeline of infection.

LIST OF INFECTION (2-6 MONTHS) AFTER TRANSPLANTATION:

Opportunistic infections:

- Toxoplasma gondii
- Pneumocystis carnii

Other infections:

- Strongyloides and other parasites species
- Fungi
- Tuberculosis

Viral infections(or its reactivation):

- Cytomegalovirus, Herpes group of virus, hepatitis B virus, hepatitis C virus.

LIST OF INFECTION AFTER SIX MONTHS OF TRANSPLANTATION:

As the immunosuppression is reduced, the amount of infection falls gradually in this sub group.

Infections in this population is similar to those in the community

- Common respiratory tract infections
- Common viral infections
- Urinary tract infections

Many viral infections not only affect the organs and grafts, but it also has some immune modulating property which predisposes to various other infections say aspergillus,Pneumocystis.[25,26,27,28]

Most patients who died in the hospital with significant liver pathological states had hepatotropic viral infections[22]. Preemptive renal transplantation, when possible, has been shown to reduce viral infections and improve survival[23].

In western India, malaria continues to be an important differential diagnosis, not only for the febrile syndrome but also for a clinical picture of rejection[24].

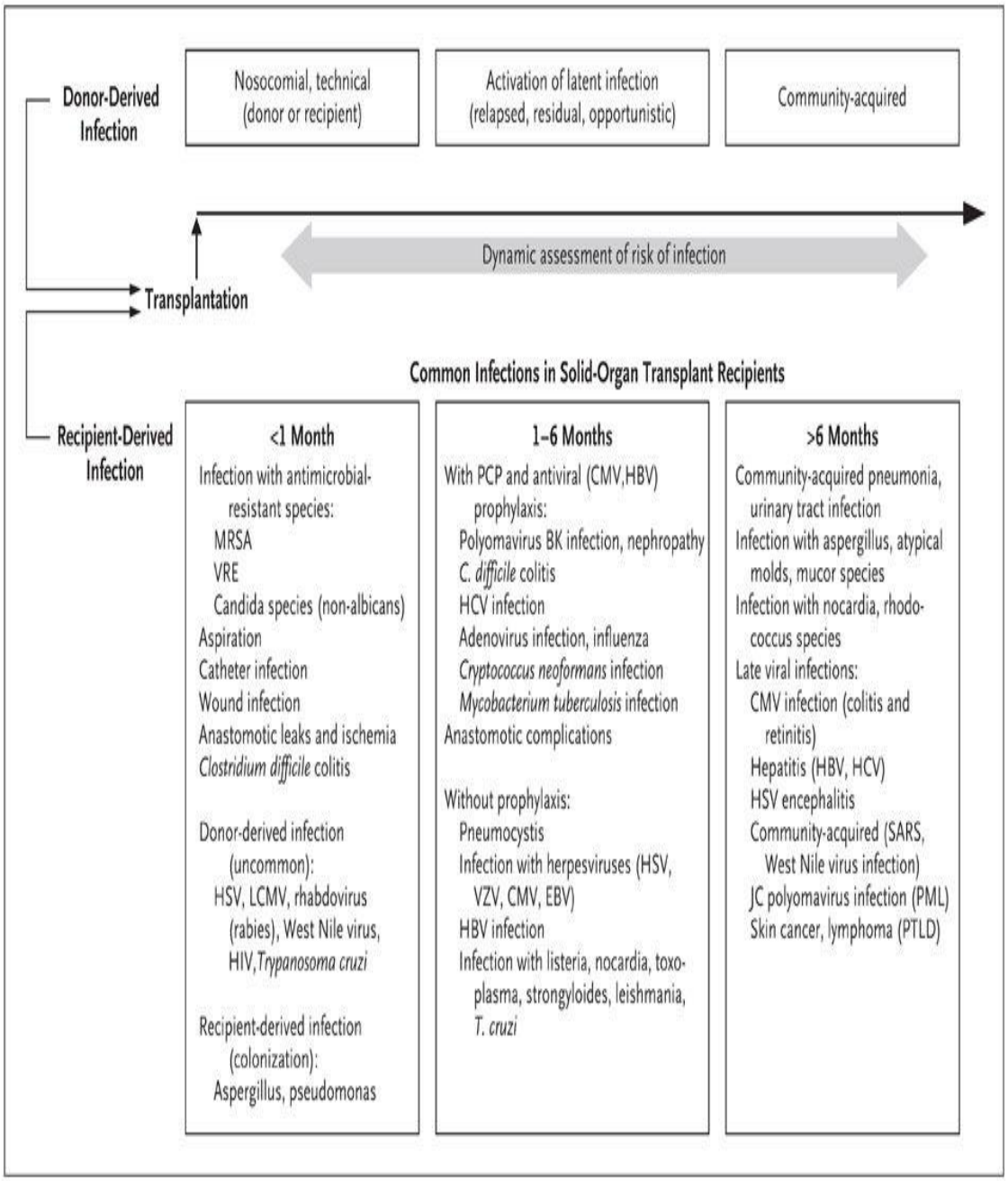


FIGURE 2: TIMETABLE OF INFECTIONS IN RENAL TRANSPLANT RECIPIENTS

Immediate post-transplant period (30days)

- Opportunistic infections are uncommon
- It takes almost a month time to effectively suppress the T cells and large dose of corticosteroid is an exception
- Vulnerable to hospital infection or transmitted through the graft.

Intermediate period (1-6months)

- Rejection episodes and infections through viruses are the major concern in this timeline.
- Adherence to time table and proper anti-infective prophylaxis effectively can avoid morbidity and mortality.
- Fungi,and parasites can surface
- Rarely polyoma virus (BK and JC) and more commonly HCV.

Late post-transplant period (>6months)

- Immunosuppression is slowly tapered and risk is on the decreasing trend.
- However with each acute rejection, timeline is reset and starts over again.
- Chronic viral infections can cause allograft injury and few of the undesirable complication listed below:
    - HCV leads to cirrhosis
    - BOOP in lungs
    - CMV leads to coronary vasculopathy
    - PTLD
    - Skin/anogenital cancers

NON INFECTIVE CAUSES OF FEVER:

GRAFT REJECTION:

It is immune mediated and can potentially present with fever. Identifying is of utmost importance as treatment is increasing immunosuppression contrary to infection where the dose of immunosuppressants needs to be reduced.

MALIGNANCY:

The most common malignancies to present with FUO are:

- Lymphoma
- Leukemia
- Renal cell carcinoma
- Hepatocellular carcinoma

DRUGS:

It is one of the common findings but often under diagnosed entity. It usually simulates an allergic or an idiosyncratic reaction. It rarely can affect the thermoregulation also.

Approximately 25% of the patients have rash and eosinophilia and hence their absence should not rule out the diagnosis[19].

The diagnosis of drug fever is made by a therapeutic trial of stopping the suspected drug (with occasional rechallenge). Most patients will defervesce within 72 hours after substituting drugs, although some may not recover for weeks. Drugs of the same class should not be reintroduced in a therapeutic trial.

Connective tissue, autoimmune, hypersensitivity diseases are less common in immunosuppressed patients

STUDY PROTOCOL

AIMS AND OBJECTIVES

1. To identify the etiology of fever in renal transplant recipient patients, to establish the existing pattern in our locality
2. To identify associations between donor, recipient factors and the etiology, if any

MATERIALS AND METHODS

Place of study: Department of Nephrology, Transplant Recipient Ward, Stanley Medical College and Hospital.

Duration: Mar 2012 to Nov 2012

Study Design: Descriptive prospective observational Study

Patient selection:

1. Any renal transplant recipient, who presents to The Dept. of Nephrology, with fever at any point in time.

Exclusion criteria:

1. Patients who are not willing to get investigated in complete.
2. Patients absconded before full evaluation

METHODOLOGY:

Transplant patients who developed fever any time after surgery will be taken into the study. Invariably, all immediate post-transplant patients will be admitted in the transplant ICU till they become stable and will be shifted to transplant recipient ward. All patients who present to us with fever in transplant OPD will be admitted to the ward and investigated, immaterial of the duration and seriousness of the illness.

- φ All the patients were enquired about the history and examined completely
- φ Initial investigations were towards the pertaining clinical clue
- φ If we do not have clinical clue, battery of tests were run keeping the cost benefit analysis in mind and the common organisms encountered based on the past experience and prevalence of the infection.
- φ Wherever possible culture and tissue demonstration is attempted.
- φ Patients were treated and followed up in the transplant OPD.
- φ Data through the above mentioned ways are collected and tabulated and analysed for the site of infection, prevalence of organisms, various interplay of host and environmental factors.
- φ A diligent attempt is made to find out non-infectious cause of fever, if any.

RESULTS

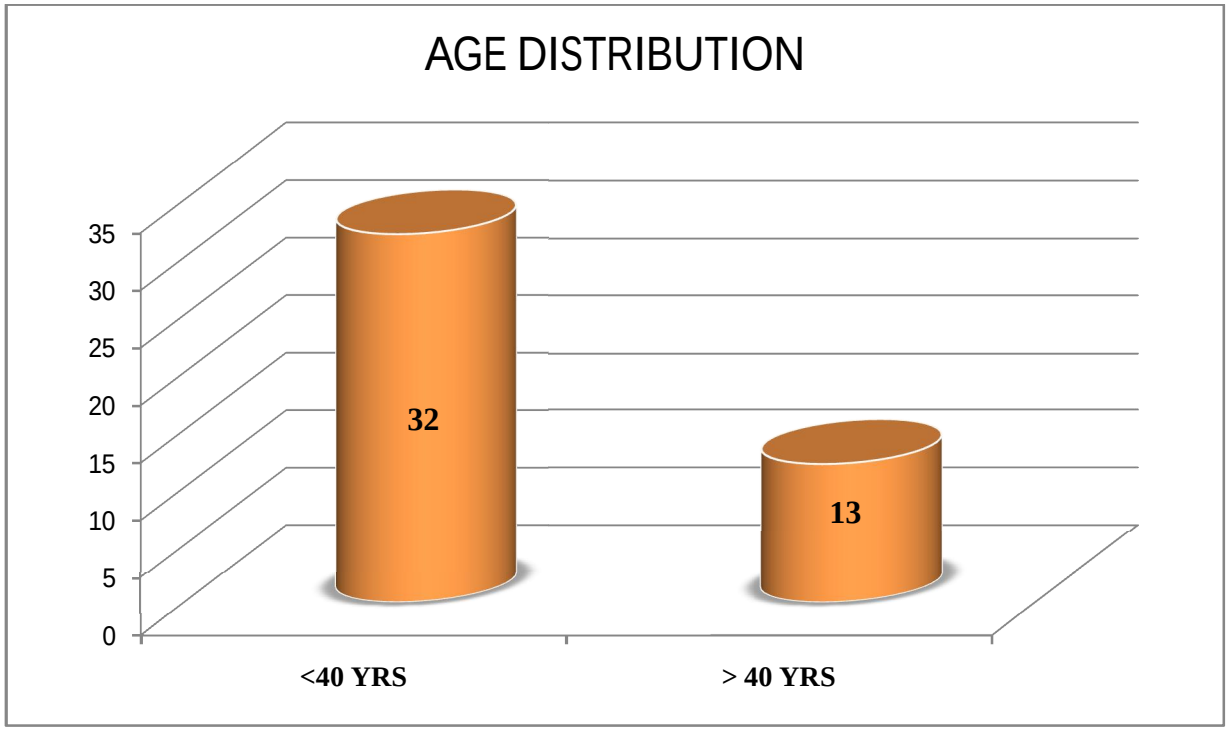
Number of fever cases in renal transplant recipients for the most part of the year in 2012 are 45. There are approximately 180 cases of transplant recipients, who are on follow up with us. This tells us the substantial morbidity of fever in renal transplantation. Fever, by itself, is an under expressed entity in these patients due to immunosuppression. So, the underlying disease which has manifested as fever is represented only like a tip of iceberg.

AGE DISTRIBUTION:

It was predominantly the younger population that presented with fever, because the number of recipients were more in the younger population. The age cut off for dividing the population is 40. Thirty two patients were younger than 40 and thirteen were over 40.

AGE DISTRIBUTION	NO OF PERSONS	PERCENTAGE
< 40 YRS	32	71.1%
> 40 YRS	13	28.9%

TABLE 2: AGE DISTRIBUTION



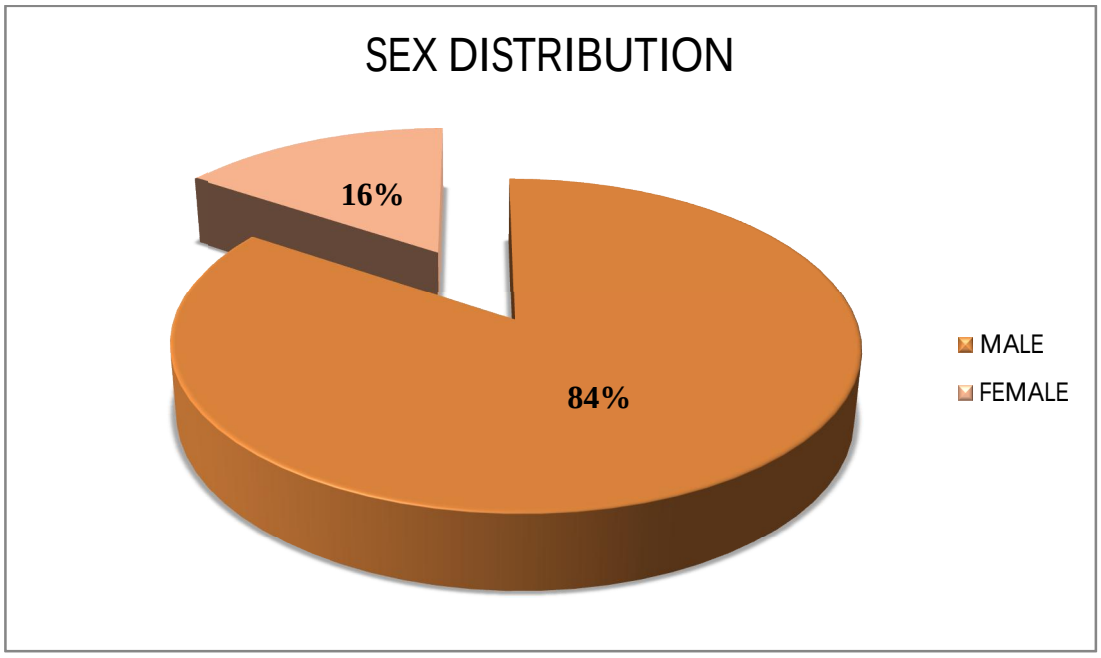
GRAPH 1: AGE DISTRIBUTION

SEX DISTRIBUTION:

SEX	NO OF PATIENTS	PERCENTAGE
MALE	38	84%
FEMALE	7	16%

TABLE 3: SEX DISTRIBUTION

Out of the 45 cases admitted with fever, there were 38 males and 7 females. The sex ratio of transplant patients in general was very adverse towards women. Interestingly, there were 9 deaths in the study and all of them were males and 5 readmissions in study period and all of them were males. There is not a single death/readmission in the female study population.



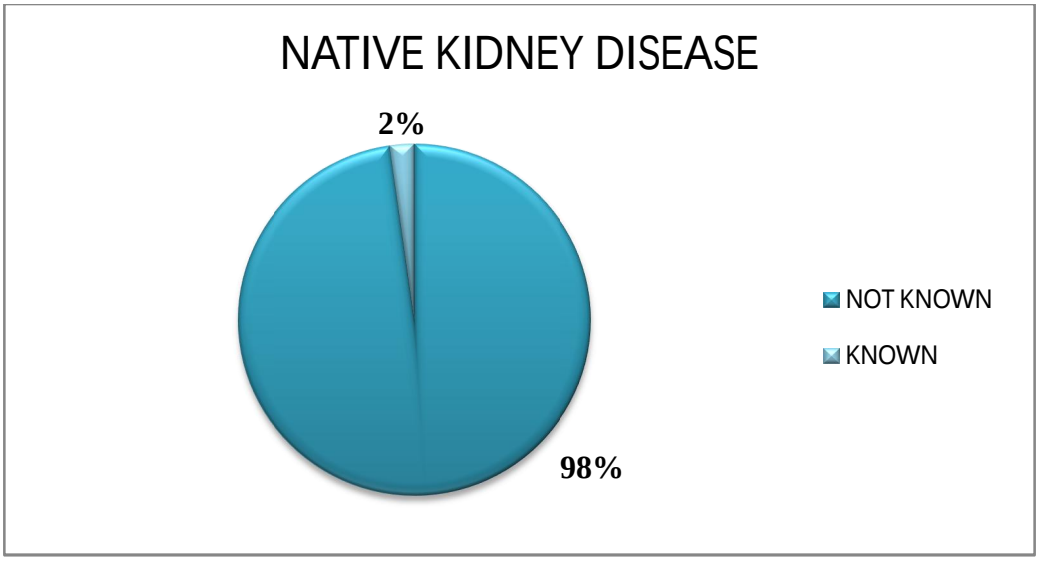
GRAPH 2: SEX DISTRIBUTION

Regarding the other parameters like pre-existing disease, epidemiological exposure, all the cases neither had a pre-existing disease nor an epidemiological exposure in the past.

NATIVE KIDNEY DISEASE DISTRIBUTION:

NATIVE KIDNEY DISEASE	NO OF PATIENTS	PERCENTAGE
NOT KNOWN	44	97.8%
KNOWN	1	2.2%

TABLE 4: NATIVE KIDNEY DISEASE



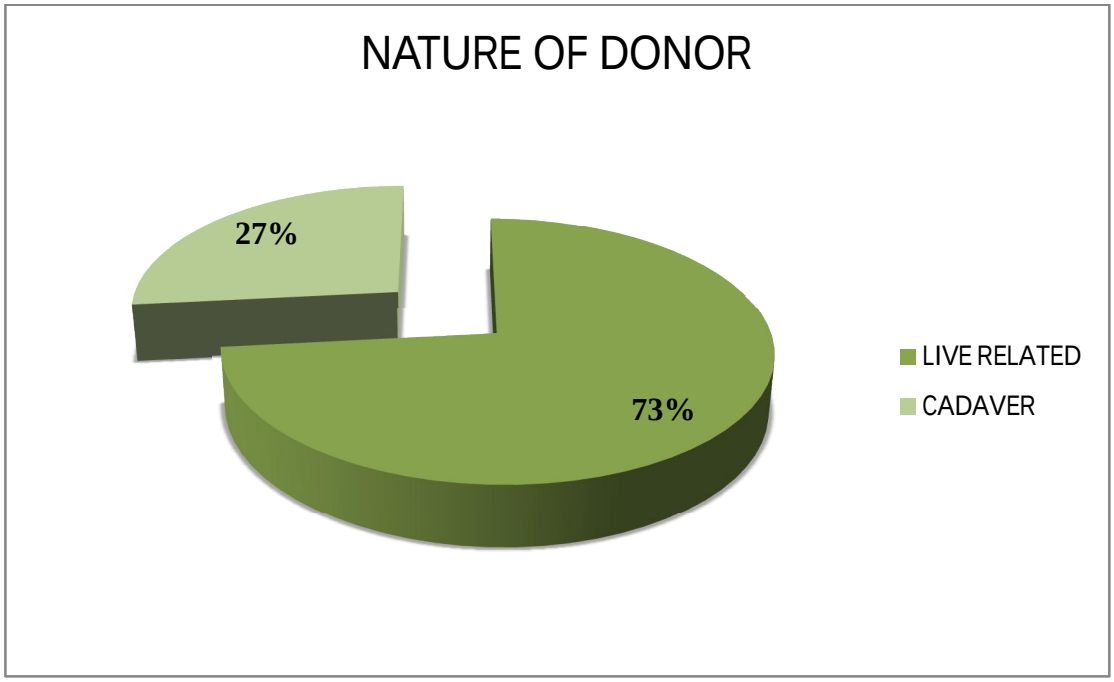
GRAPH 3: NATIVE KIDNEY DISEASE

Only 1 out of the 45 patients had a known native kidney disease prior to transplant. The patient had Anti GBM disease and that accounts for 2% in the study.

NATURE OF DONOR:

NATURE OF DONOR	NO OF PATIENTS	PERCENTAGE
LIVE RELATED	33	73.3%
CADAVER	12	26.7%

TABLE 5: NATURE OF DONOR



GRAPH 4: NATURE OF DONOR

In the study, we had 33 recipients from live related donor and 12 from cadaveric donors. Surprisingly, 8 deaths were recipients from live related donors out of 9 deaths. We had 5 readmissions, out of which 3 were from live related renal transplants and 2 were from cadaveric renal transplant.

TREATMENT FOR REJECTION:

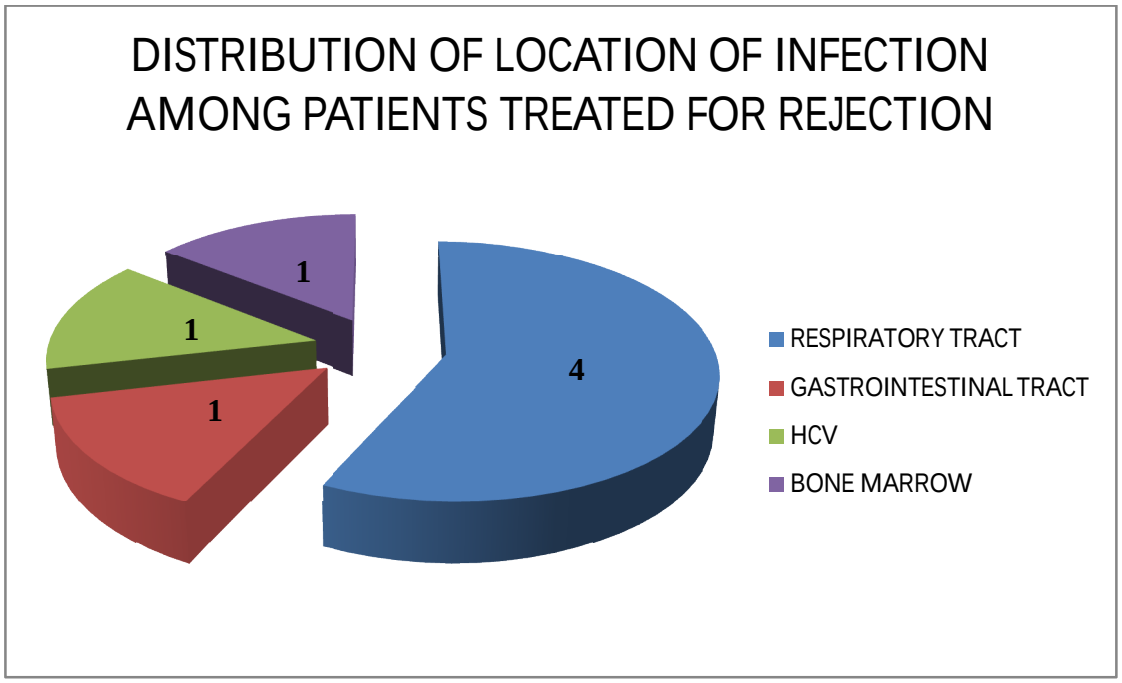
Among the fever patients, seven were treated for acute rejection at least once during the post-transplant period.

A table that classifies the involvement of organ system is represented below:

LOCATION	NO OF PERSONS TREATED FOR REJECTION EARLIER	PERCENTAGE
RESPIRATORY TRACT	4	57.1%
GASTRO INTESTINAL TRACT	1	14.3%
HCV	1	14.3%
BONE MARROW	1	14.3%

TABLE 6: TREATMENT FOR REJECTION

Majority of the patients who had fever and who had treatment for rejection had respiratory tract infection. Gastrointestinal manifestation, bone marrow involvement and viremia were noticed in three patients (one in each).



GRAPH 5: DISTRIBUTION OF LOCATION OF INFECTION AMONG PATIENTS TREATED FOR REJECTION

One patient succumbed to death out of the four of respiratory tract infection.

LEVEL OF TACROLIMUS:

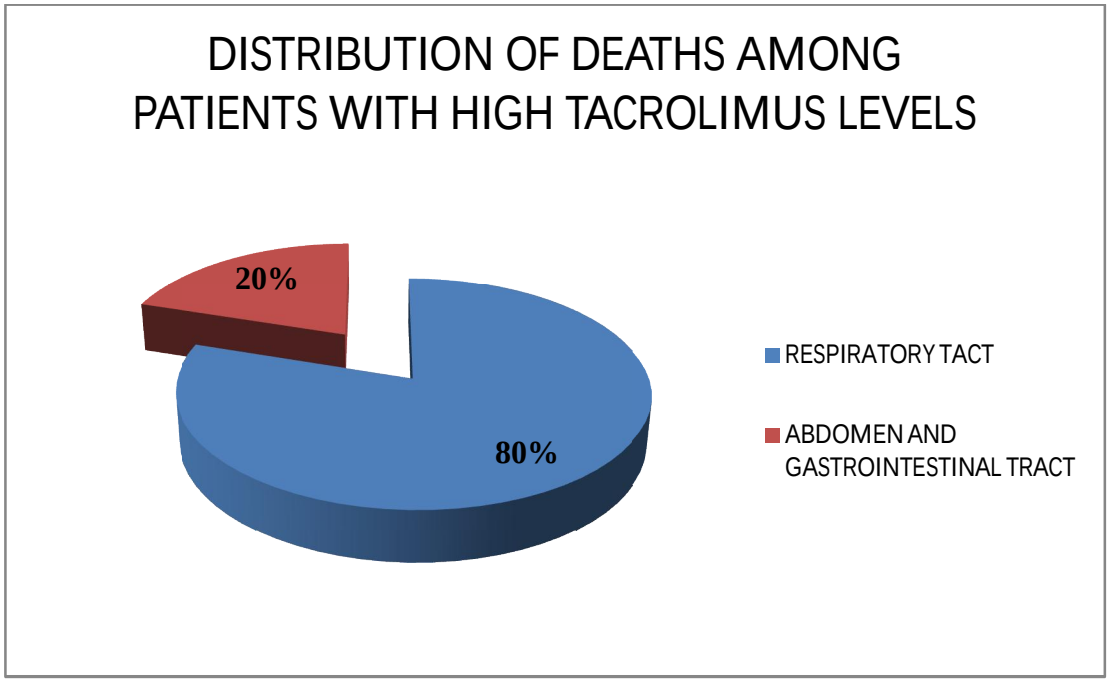
All the patients were under triple immune suppression with prednisolone, tacrolimus and mycophenolate mofetil. We routinely check tacrolimus levels for any patient with fever and / or unexplained decrease in graft function. We could not check mycophenolate mofetil levels due to financial constraints.

In this study 16, patients had high tacrolimus levels, which is just over one third of the patients. Rest had their levels in the therapeutic range.

LOCATION OF INFECTION	NO OF PATIENTS	PERCENTAGE
RESPIRATORY TRACT	9	56.25%
ABDOMEN AND GASTROINTESTINAL	4	25%
SEPSIS WITH NO OTHER FOCUS	1	6.25%
TUBERCULOSIS OF BONE MARROW	1	6.25%
UNDIAGNOSED	1	6.25%

TABLE 7: FOCUS OF INFECTION AMONG THOSE WITH HIGH TACROLIMUS LEVELS

Nine out of sixteen patients with high tacrolimus levels had a respiratory focus of infection. Four had their source in the abdomen and the rest had one case each.



GRAPH 6: DISTRIBUTION OF DEATHS AMONG PATIENTS WITH HIGH TACROLIMUS LEVELS

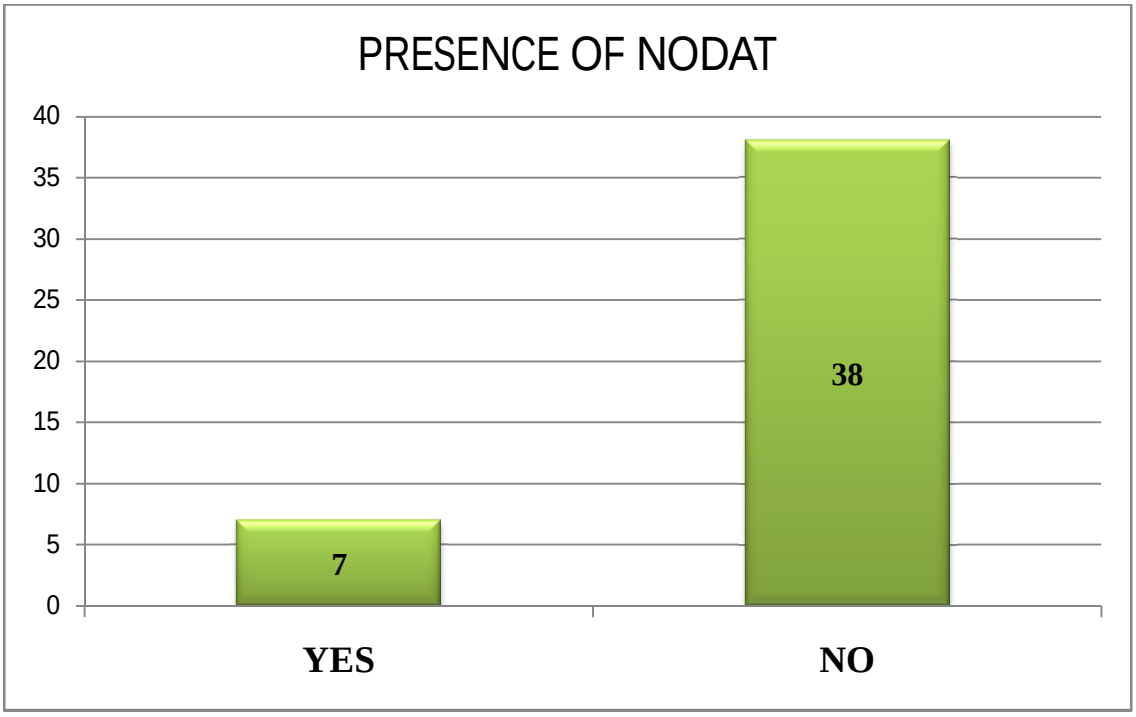
Eighty percent (4) of the patients who died along with high tacrolimus levels were due to respiratory tract infections. The remaining 20% (1) of the patients died of gastrointestinal involvement.

There was no difference among the patients in vaccination and Pneumocystis carnii prophylaxis, as all of them were adequately vaccinated and were adherent to pneumocystis prophylaxis.

NODAT (New onset diabetes after transplant):

PRESENCE OF NODAT	NO OF PATIENTS	PERCENTAGE
YES	7	15.6%
NO	38	84.4%

TABLE 8: PRESENCE OF NODAT



GRAPH 7: PRESENCE OF NODAT

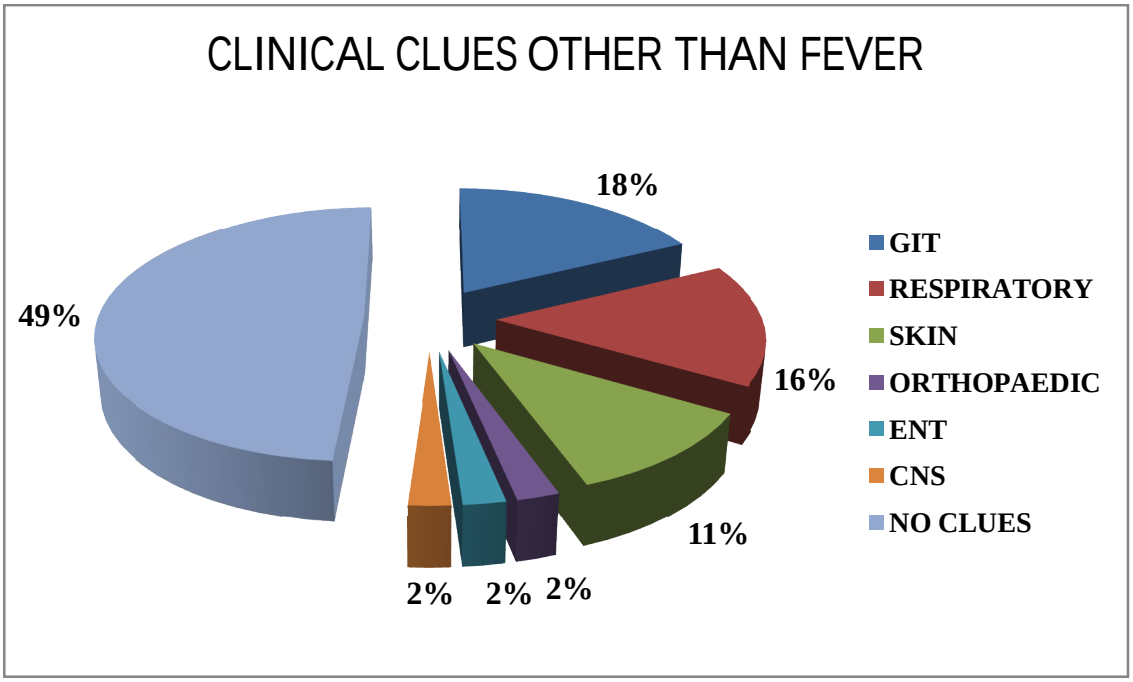
We observed, 7 patients had NODAT out of the 45. One patient who died due to the disease had a co-existing NODAT.

CLINICAL CLUES:

Transplanted patients are tightly immunosuppressed to avoid rejection. In the process, clinical clues become thinner and thinner. It is good to look back and find out the spectrum of signs, symptoms and the system involved. Indeed, they are overwhelming signs despite immunosuppression.

SYSTEM WISE MANIFESTATION	NO OF PERSONS
GIT	8
RESOIRATORY	7
SKIN	5
ORTHOPAEDIC	1
ENT	1
CNS	1
NO CLUES	22

TABLE 9: CLINICAL CLUES



GRAPH 8: CLINICAL CLUES

A striking fact in the chart is 49% of the patients did not have any clinical clue to pinpoint investigations. Gastrointestinal tract, respiratory tract and skin manifestations are the next common systems involved in descending order.

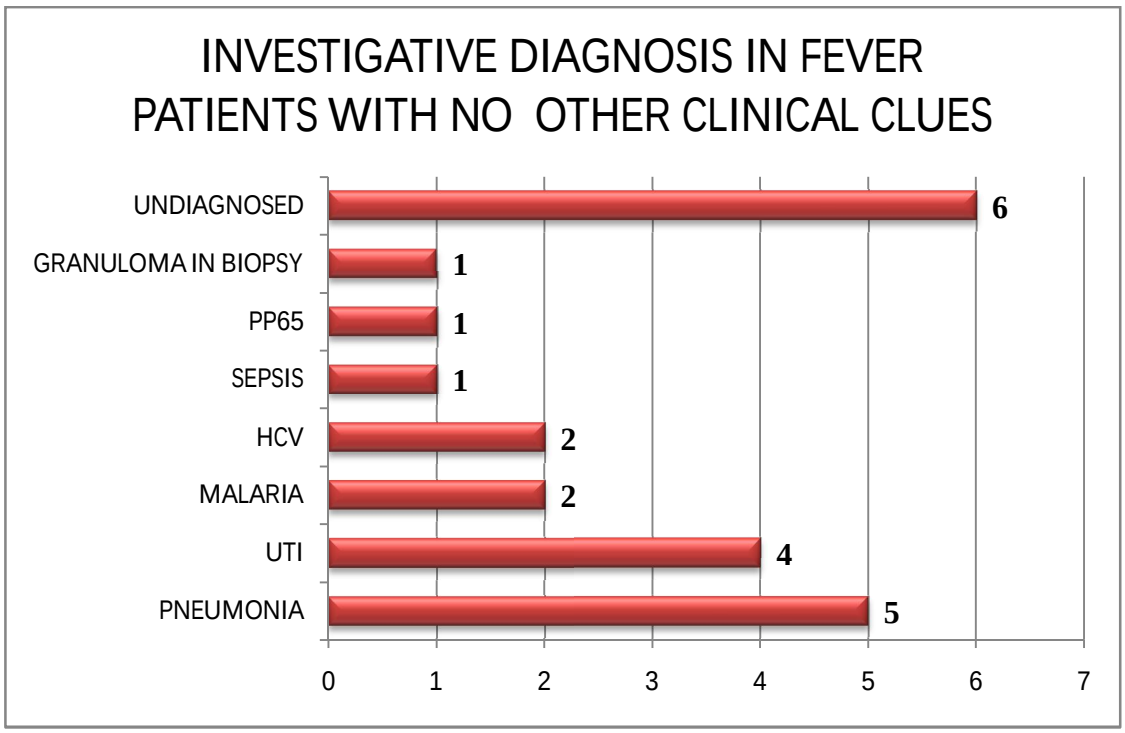
We had one case each with clinical clue in ENT, ORTHOPAEDICS, CNS.

Retrospectively analysing all these patients, without any other clue after investigation, revealed etiologies in most of them.

INVESTIGATIVE DIAGNOSIS IN CLINICALLY MUTE PATIENTS OTHER THAN FEVER	NO OF PERSONS	PERCENTAGE
UNDIAGNOSED	6	27.3%
PNEUMONIA	5	22.7%
UTI	4	18.3%
MALARIA	2	9.1%
HCV	2	9.1%
SEPTICEMIA WITHOUT FOCUS	1	4.5%
PP 65	1	4.5%
TB GRANULOMA IN BONE MARROW	1	4.5%

TABLE 10: INVESTIGATIVE DIAGNOSIS IN CLINICALLY MUTE PATIENTS

Still in patients who did not have any other clue, a majority of the patients remained undiagnosed, even after investigating.



GRAPH 9: INVESTIGATIVE DIAGNOSIS IN CLINICALLY MUTE PATIENTS

We can see the majority of the patients, with no other clue were undiagnosed even after investigations. Next common diagnosis is pneumonia, followed by urinary tract infections. Malaria, HCV, sepsis, PP65, Granuloma are other investigations contributing to the list in descending order.

HIERACHY OF USEFUL INVESTIGATIONS IN PATIENTS WITH NO OTHER CLINICAL CLUES:

1. CT CHEST

2. URINE CULTURE AND SENSITIVITY

3. QUANTITATIVE BUFFY COAT

4. HCV RNA

5. BLOOD CULTURE AND SENSITIVITY

6. PP 65

7. BONE MARROW ANALYSIS

ANALYSIS OF INVESTIGATIONS:

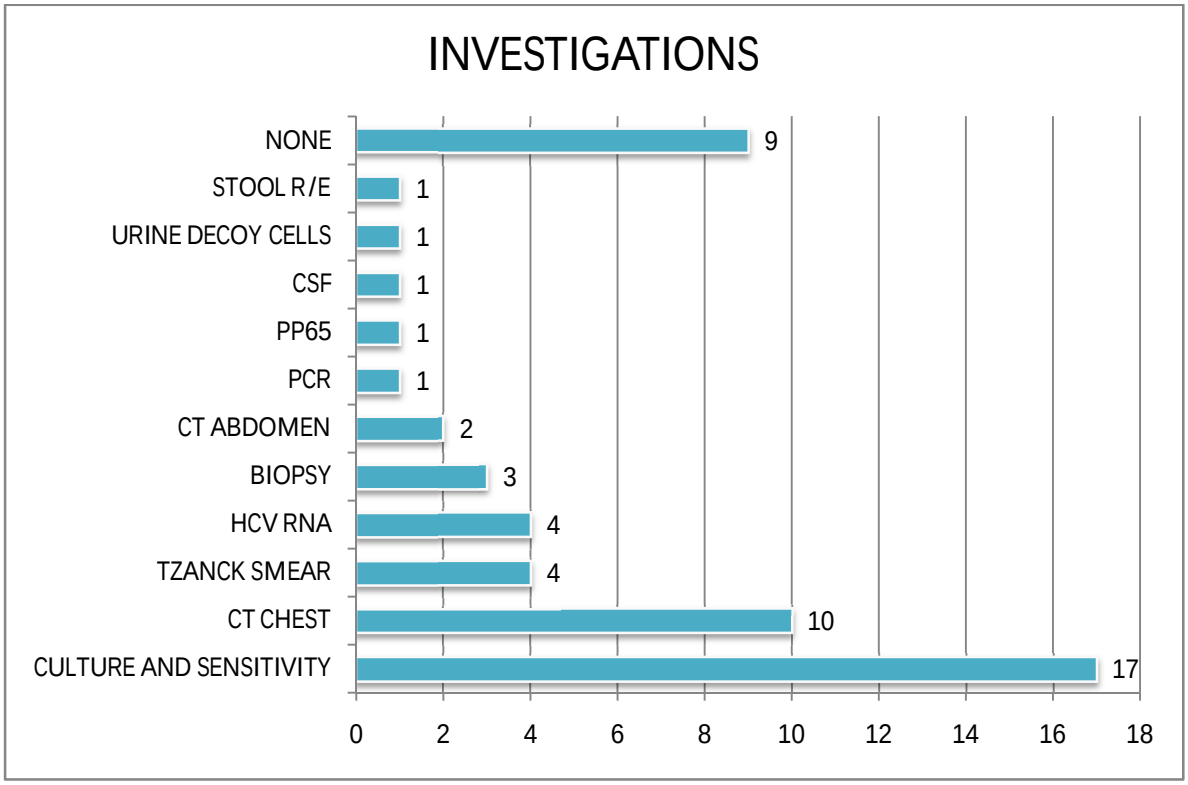
Investigations are very important in evaluating any patient. There are situations in which clinical scenario can be masquerading or muted. One such situation is immunosuppression.

The number of investigations and the number of patients don’t tally here as one patient requires more than one investigation to arrive or conclude at a diagnosis.

Hence it is of utmost importance and worthwhile to rewind and have a good look at the investigations that helped us.

INVESTIGATIONS	NO OF CASES	PERCENTAGE
CULTURE AND SENSITIVITY	17	31.4%
CT CHEST	10	18.4%
TZANCK SMEAR	4	7.4%
HCV RNA	4	7.4%
BIOPSY	3	5.6%
CT ABDOMEN	2	3.7%
PCR	1	1.9%
PP65	1	1.9%
CSF ANALYSIS	1	1.9%
STOOL ROUTINE	1	1.9%
URINE DECOY CELLS	1	1.9%
NONE	9	16.6%

TABLE 11: ANALYSIS OF INVESTIGATIONS



GRAPH 10: ANALYSIS OF INVESTIGATIONS

It is striking that culture and sensitivity, is the predominant yielding investigation in the study, which will be the same in any study in which disease is predominantly caused by an infectious agent.

Next to culture, it was CT chest that gave clue to the disease in 10 individuals. 9 patients remained undiagnosed at the end of investigations.

Tzanck smear, HCV RNA, biopsy, CT abdomen, PCR, PP 65,csf analysis, urine decoy cells, stool routine are the other investigations that revealed clue to the underlying disease in descending order.

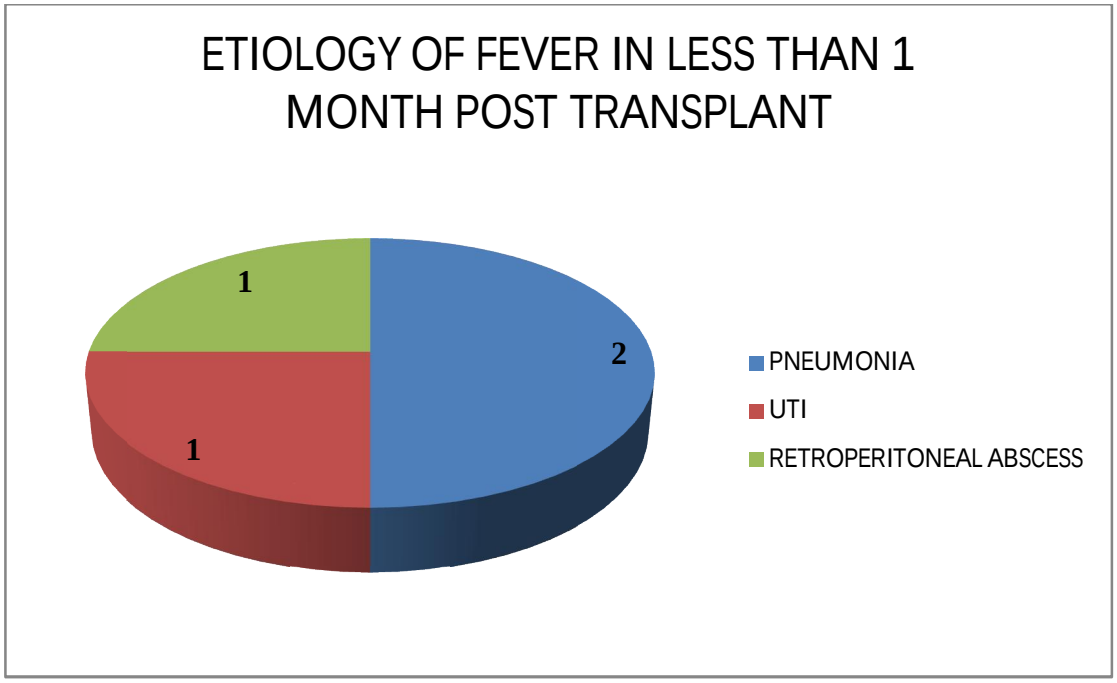
Infections in renal transplant recipients are classically classified essentially into 3 different categories.

1. Infection less than 1 month
2. Infection between 1 - 6 months
3. Infection more than 6 months

This classification helped us understand how a renal transplant recipient succumbing to infection is similar or different from a normal human succumbing to infection. This was proposed by **Rubin et al**. There are Indian data which had modified the time table as per prevalence in our country.

INFECTION LESS THAN 1 MONTH:

Infections less than 1 month are usually no different than any other normal person. The predominant infections are post operative and hospital acquired infections, in our study.



GRAPH 11: ETIOLOGY OF FEVER IN LESS THAN 1 MONTH POST-TRANSPLANT

INFECTIONS LESS THAN 1 MONTH	NO OF PERSONS	PERCENTAGE
PNEUMONIA	2	50%
UTI	1	25%
RETROPERITONEAL ABSCESS	1	25%

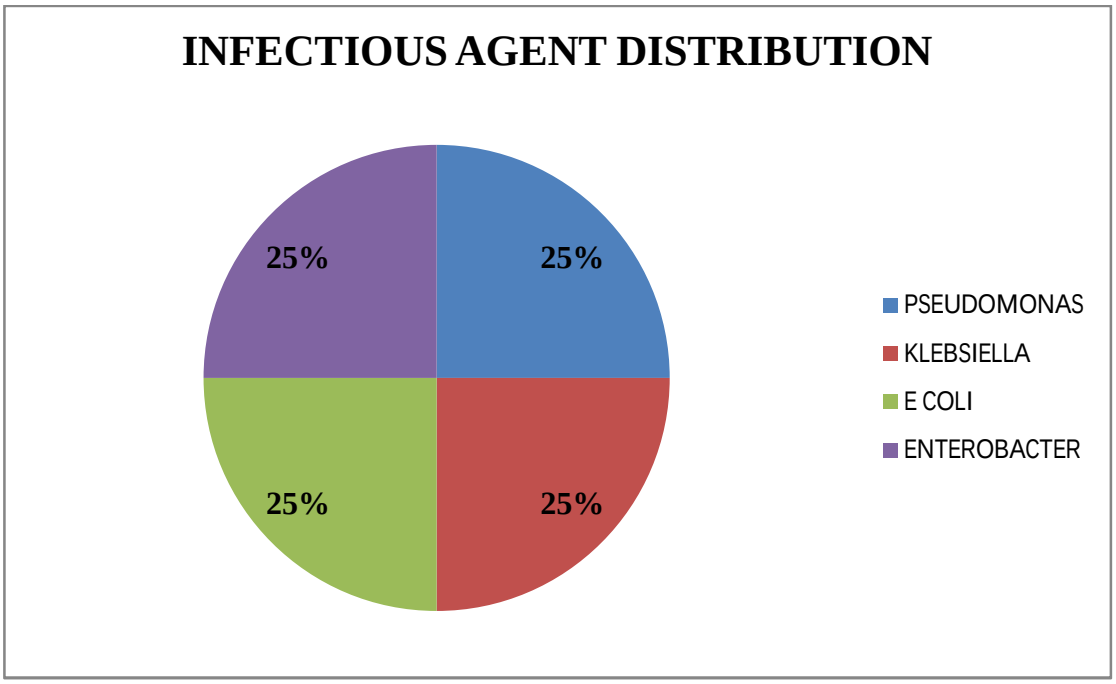
TABLE 12: ETIOLOGY OF FEVER INLESS THAN 1 MONTH POST-TRANSPLANT

Out of the 4 cases in the post-transplant period 2 are pneumonia, 1 urinary tract infection and 1 retro peritoneal abscess. All 4 cases are either operative complication or hospital acquired infections.

Analyses of the infective etiology are discussed below.

ORGANISM	NO OF PERSON	PERCENTAGE
PSEUDOMONAS	1	25%
KLEBSIELLA	1	25%
E COLI	1	25%
ENTEROBACTER	1	25%

TABLE 13: ANALYSIS OF INFECTIVE ETIOLOGY



GRAPH 12: ANALYSIS OF INFECTIVE ETIOLOGY

We had one case each of pseudomonas, Klebsiella, E coli, Enterobacter.

INFECTIONS BETWEEN 1 – 6 MONTHS:

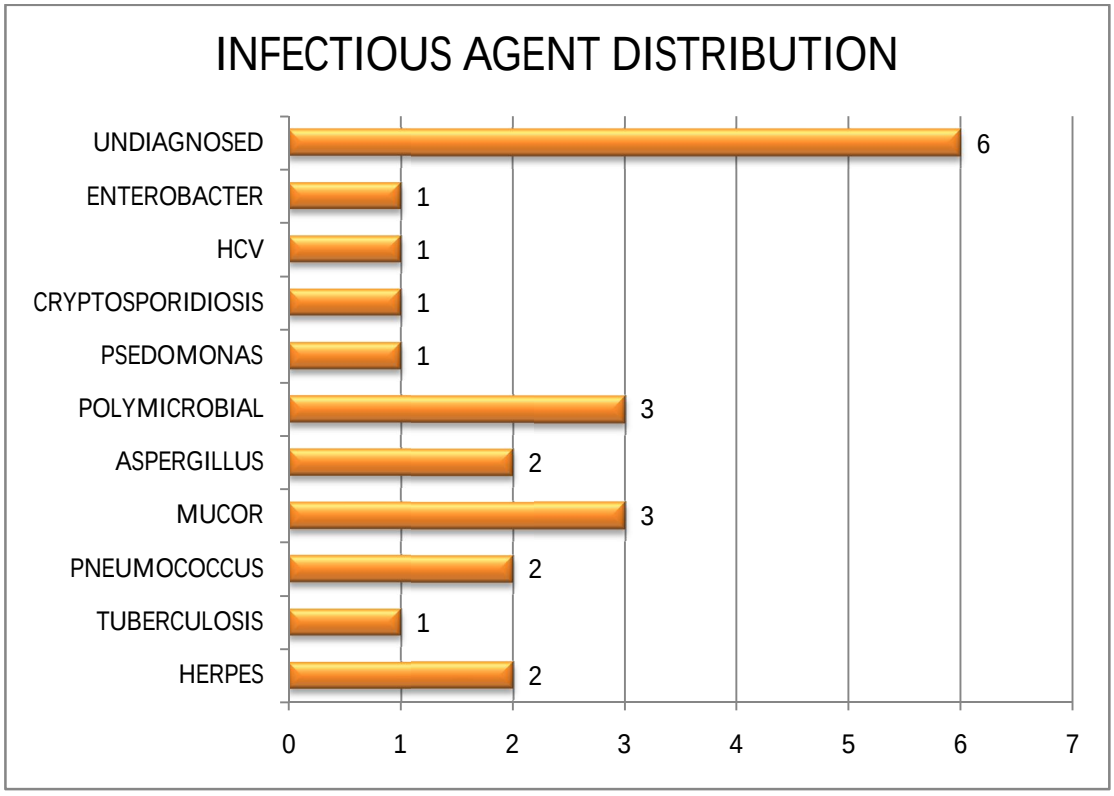
INFECTIOUS FOCI AND LOCATION	NO OF PERSONS	PERCENTAGE
PNEUMONIA AND LUNG ABSCESS	8	34.9%
SKIN;HERPES	2	8.7%
MALARIA	2	8.7%
WRIST;TUBERCULOSIS	1	4.3%
RETROPERITONEAL ABSCESS	1	4.3%
GI TRACT ; CRYPTO SPORIDIOSIS	1	4.3%
HCV	1	4.3%
POLYMICROBIAL SEPSIS WITHOUT FOCUS	1	4.3%
UNDIAGNOSED	6	26.2%

TABLE 14: ETIOLOGY OF FEVER IN BETWEEN 1- 6 MONTH POST-TRANSPLANT

DISTRIBUTION OF THE INFECTIOUS AGENT

INFECTIONS	NO OF PERSONS	PERCENTAGE
HERPES	2	8.8%
TUBBERCULOSIS	1	4.3%
PNEUMOCOCCUS	2	8.8%
MUCORMYCOSIS	3	13%
ASPERGILLUS	2	8.8%
POLYMICROBIAL	3	13%
PSEUDOMONAS	1	4.3%
CRYPTOSPORIDIOSIS	1	4.3%
HCV	1	4.3%
ENTEROBACTER	1	4.3%
UNDIAGNOSED	6	26.1%

TABLE15: INFECTIOUS AGENTS IN FEVER BETWEEN 1-6 MONTH POST-TRANSPLANT



GRAPH 13: INFECTIOUS AGENTS IN FEVER BETWEEN 1- 6 MONTH POST-TRANSPLANT

Almost one quarter of the patients, with fever between 1 – 6 months post-transplant did not have any identifiable agent.

Among the agents that were identified, the most common agents were Mucor and poly microbial infections. Both of them, contributing to 13% independently. The next common organisms are Herpes, Pneumococcus and Aspergillus and each of them contributed to around 9%.Tuberculosis has been identified in 5% of the population and the rest of the organism contributed to 4% each.

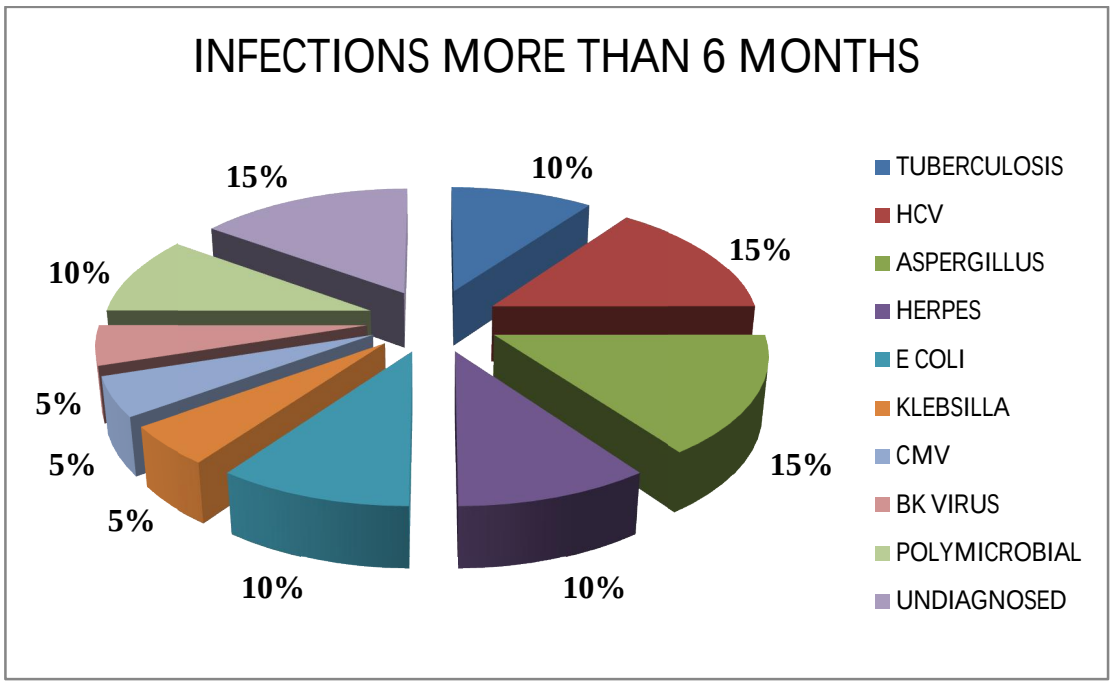
INFECTIONS IN RECIPIENTS MORE THAN 6 MONTHS:

There were 19 patients in this group. List of systems involved and organism involved are depicted below.

INFECTIONS (FOCUS)	NO OF PERSONS
UTI	3
LIVER AND GI TRACT(HCV)	3
RESPIRATORY TRACT(PNEUMONIA)	3
ENT	2
SKIN;HERPES	2
CNS	1
CMV VIREMIA	1
BONE MARROW(TUBERCULOSIS)	1
UNDIAGNOSED	3

TABLE16: ETIOLOGY OF FEVER INMORE THAN 6 MONTHS POST-TRANSPLANT

A quick look into the infections those are responsible for fever more than 6 months are projected below.



GRAPH 14: ETIOLOGY OF FEVER IN MORE THAN 6 MONTHS POST-TRANSPLANT

There are 3 splits in the picture sharing 15% each contributing to the majority of the infections. They are HCV, Aspergillosis, and the infections in the last split could not be cracked and hence remained undiagnosed.

Herpes, polymicrobial infections and E coli are the other infections that contributed to 10% of the infections. BK virus, CMV, Klebsiella contributed to 5% each.

MIXED INFECTONS:

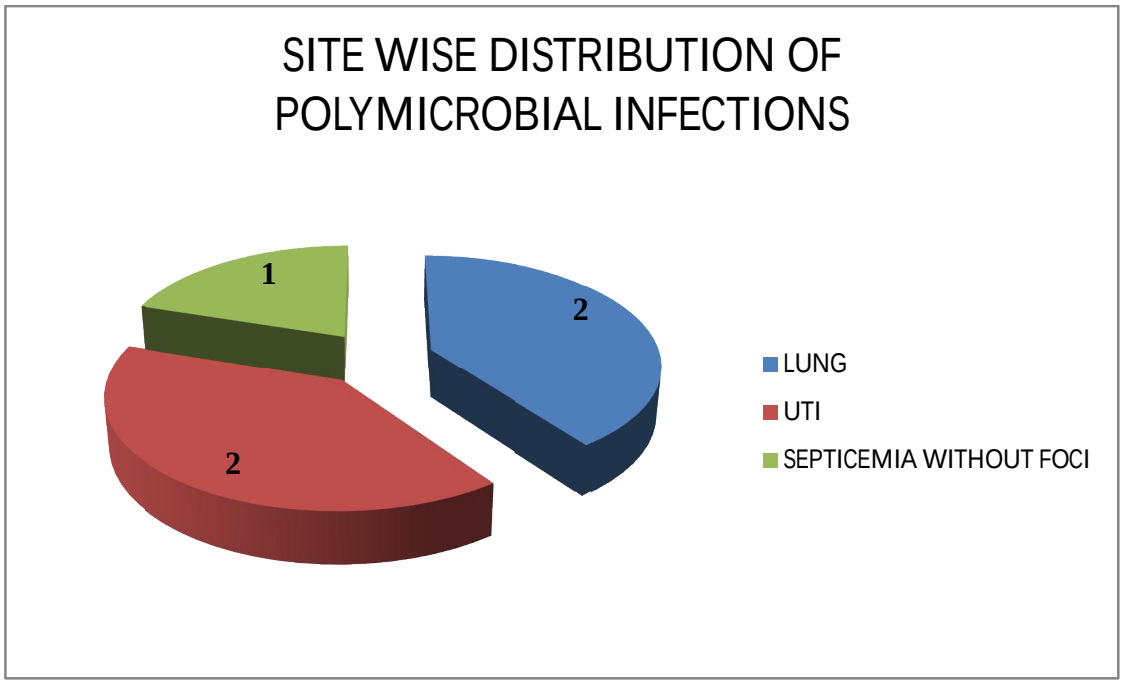
Among the patients infected, there are 5 polymicrobial infections. There were no mixed infections in less than one month group. There were three polymicrobial infections in 1 – 6 months group and 2 in more than 6 months group.

MONTHS AFTER TRANSPLANT	LESS THAN ONE	BETWEEN ONE TO SIX	MORE THAN SIX
NO OF CASES	NIL	3	2
PERCENTAGE	0%	60%	40%

TABLE 17: DISTRIBUTION OF MIXED INFECTIONS WITH RESPECT TO POST-TRANSPLANT DURATION

The organisms that are detected in polymicrobial infections are Pseudomonas, Klebsiella, Aspergillus and E.coli.

It is also prudent to discuss the site of polymicrobial infections.



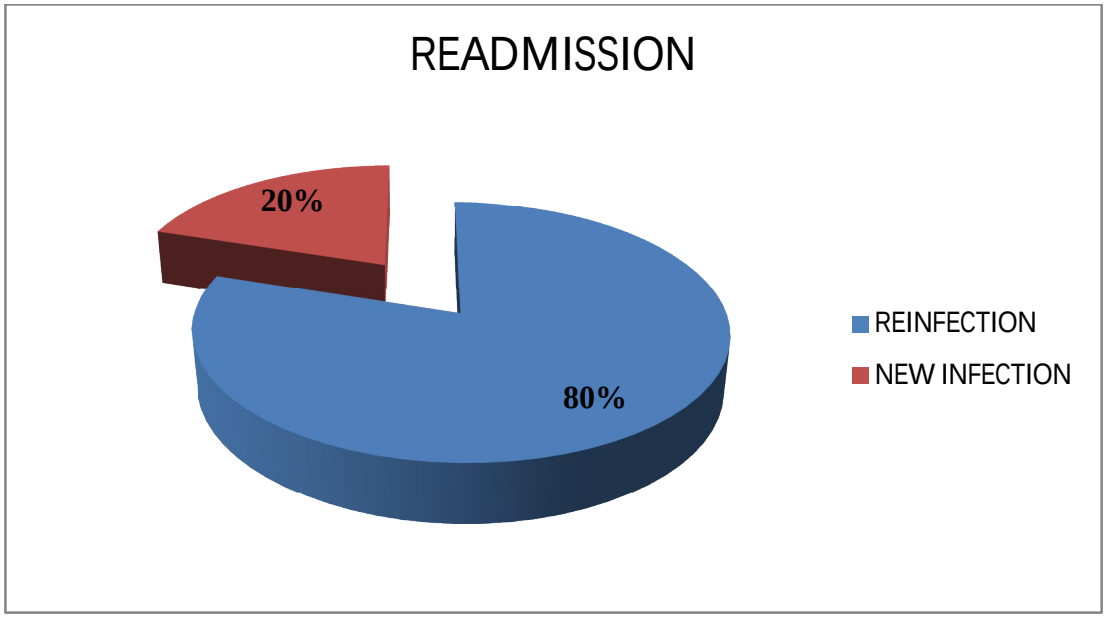
GRAPH 15: SITEWISE DISTRIBUTION OF POLYMICROBIAL INFECTIONS

Distribution of polymicrobial infections based on location revealed lung and urinary tract infections in 80% of the patients (sharing 40% each). One individual had polymicrobial sepsis identified in blood culture, with no other recognizable primary focus of infections.

A very important observation is all polymicrobial infections between 1-6 months succumbed to infection (accounts for 60% polymicrobial infections).

READMISSIONS:

- Out of 45, 5 had readmissions.
- All 5 of them are males.
- Four on five of them had reinfection with the same organism.
- Fifth patient was infected with a different organism
- Three of them had infection less than 1 month and next episode cropped up between 1 – 6 months.
- Two patients died during readmissions.
- One patient is still in the premises and getting treated intensively.
- Etiology was not diagnosed in one and he succumbed to the disease.

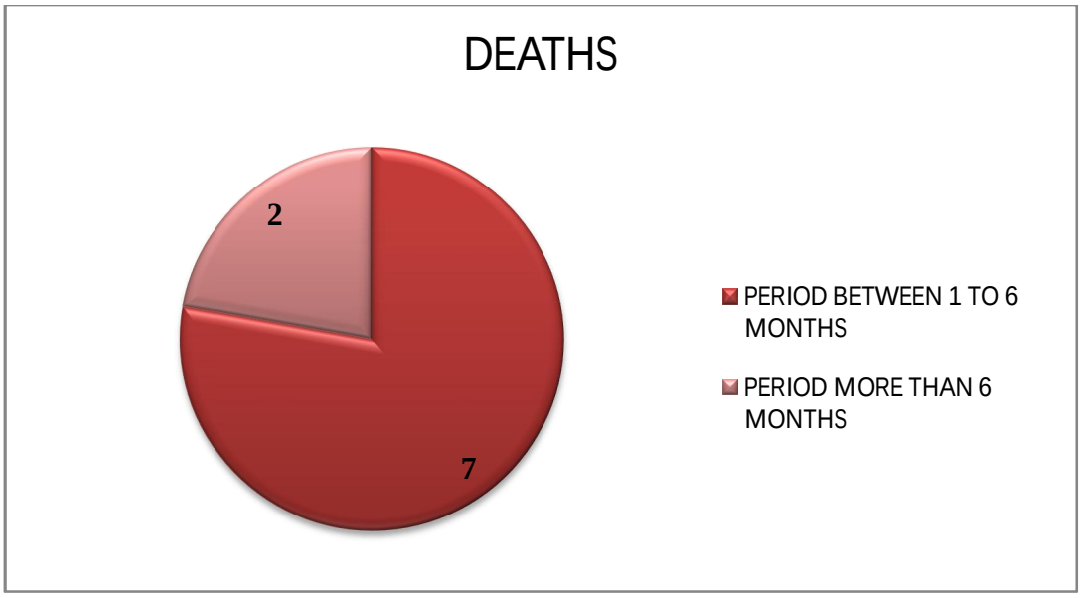


GRAPH 16: READMISSION

MORTALITY:

- A very disappointing fact is that 9 out of 45 patients died.
- It accounts for 20% of the cases admitted with fever, which is a striking fact that tells us the very importance of fever in renal transplants
- All 9 of them were males.
- Two patients who had readmission died.

Seven out of nine were between one to six months post transplant. Two out of nine were in the category of more than 6 months post transplant.



GRAPH 17: MORTALITY PATTERN

It is very important to review the site and organism that had been implicated for mortality.

SITE

SITE OF INFECTION	DEATHS	PERCENTAGE
RESPIRATORY TRACT	6	66.7%
CNS	1	11.1%
ISOLATION IN BLOOD ALONE(WITH NO OTHER FOCUS)	1	11.1%
UNDIAGNOSED	1	11.1%

TABLE 18: DEATH RATE WITH RESPECT TO SITE OF INFECTION

Lung infections are the most common cause of death in the study accounts for 66% of the deaths. The other 33% of deaths are shared as mentioned in the table.

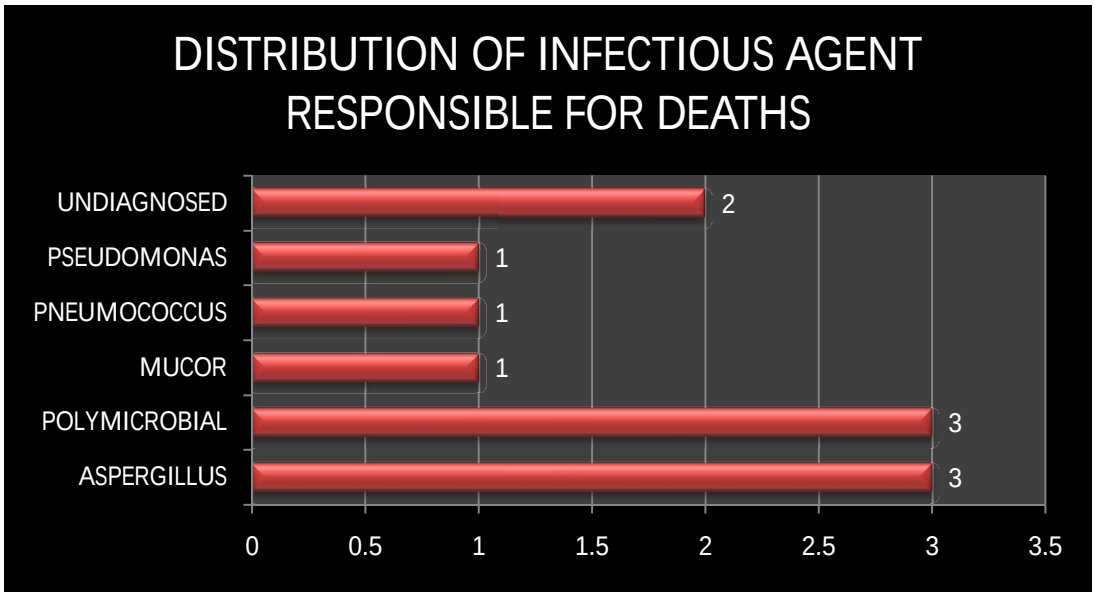
Lung involvement always had been too aggressive. It neither gave time to the patient nor to the treating physician. It was very difficult site to handle since many had hemoptysis and the alveoli were drowned in their own blood hampering the respiratory exchange.

INFECTIVE AGENT DISTRIBUTION:

The number of agents and the number of deaths will not match due to polymicrobial infections.

INFECTIOUS AGENTS RESPONSIBLE FOR DEATH	NUMBER OF DEATHS	PERCENTAGE
ASPERGILLUS	3	27.3%
POLYMICROBIAL	3	27.3%
MUCOR	1	9.1%
PNEUMOCOCCUS	1	9.1%
PSEUDOMONAS	1	9.1%
UNDIAGNOSED	2	18.1%

TABLE 19: DEATH RATE WITH RESPECT TO INFECTIVE AGENT



GRAPH 18: DISTRIBUTION OF INFECTIOUS AGENT RESPONSIBLE FOR DEATHS

- All polymicrobial infections between 1 – 6 months died
- All aspergillus pneumonia ended up in the mortality list.
- Mucor, pneumococcus, pseudomonas were responsible for 1 death each.
- There were two deaths, in which we failed to diagnose the etiology.

SUMMARY OF RESULTS

- We have around 180 post transplant patients in routine follow up with us in our Department of Nephrology.
- Forty five patients were admitted with fever during study period
- Seventy one percent of the patients were less than forty years and twenty nine percent were more than forty years.
- Eighty four per cent of them were males and sixteen percent were females.
- A high proportion of young and male population may be secondary to the increasing in number of transplant correspondingly in that subgroup.
- Only one patient's native kidney disease was known in the whole population
- Seventy three percent of the population had live related donors and twenty seven percent had cadaveric donors.
- Seven patients were treated for rejection and fifty seven percent of them had respiratory infection.

- Sixteen patients had their tacrolimus values higher than the therapeutic range and fifty seven percent of them had respiratory infections

- All of them were properly immunized and were compliant with Pneumocystis prophylaxis.

- None of them had a significant environmental exposure or a pre-existing disease.

- Fifteen percent of the patients have NODAT.

- Most of the patients presenting with fever, had no other clinical signs and symptoms(forty nine percent)

- When investigated, twenty three percent had lung infections, eighteen percent had urinary tract infection and twenty seven percent remain undiagnosed

- Excluding culture and sensitivity (31.4%), CT chest (18%) was the next productive tool of investigation.

- Early post-transplant infections (less than 1 month) are all hospital acquired infections, contributing to four cases

- In the above category, fifty per cent of them are pneumonia. UTI and surgical site infection accounted for twenty five percent each.

- Intermediate post-transplant group (1 – 6 months) had diverse etiology, with lung infections attributing to thirty five percent and twenty six percent remain undiagnosed.

- In the above group, mucor and polymicrobial infection contributed to thirteen percent each, whereas herpes, pneumococcus, aspergillus contributed to nine percent each.

- Late post-transplant infections(more than 6 months), are involving predominantly urinary tract, gastro intestinal tract and respiratory tract

- In the above category aspergillus, hepatitis c virus, undiagnosed are the major problems accounting for 15% each, followed by tuberculosis, herpes, e coli and polymicrobial infections accounting for 10% each.

- Overall, five patients had mixed infections (nil in the early transplant group, three in the intermediate group and two in the late infections group).

- All polymicrobial infections in the intermediate group succumbed to infections and died.

- We had five readmissions and four of them had reinfection with the same organisms, while one had infection with a different organism.

- There were nine deaths among the study group, which accounted for 20%.

- All of them were males and five of them had high tacrolimus levels.

- The predominant site of infection among the deceased is lung (67%) and the predominant infections amongst them are aspergillus and mixed infections (27% each).

DISCUSSION

Fever in renal transplant recipients is interesting and invaluable as it has a great say in the outcome of the patient. In general, infection in patients with renal transplant are much less, when compared to other organ transplants. The widely accepted reason is, renal transplant is an elective or semi elective procedure, whereas the clinical and nutritional status of the patient in other transplants is much worse[32]

We had a higher number of men in the study and in the mortality list probably due to higher number of transplants among men. Other demographic data did not yield much. This is similar to the Indian study by **Ram et al** where the death is not influenced by age or sex[32]. All of them were under immune suppression with prednisolone, tacrolimus, and mycophenolate mofetil and were strictly adherent to pneumocystis prophylaxis.

We had seven patients with NODAT and one in this category died. Seven patients were treated for rejection and 57% of them had involvement in the lungs. More than one third of the patients had high tacrolimus levels and 57% had lung infections.

A large percentage (49%), had clinically no other clue in the history or examination for localizing the site or the organisms. Rest of the population were diagnosed by diligent and systematic investigations. After localizing the site of infection culture and sensitivity happened to be the best tool and to localize the site, CT chest was the most productive investigation.

Regarding the infections in the early transplant period, our results are very similar to the results in the western literature and Indian studies by **Rubin et al** and the study from CMC Vellore by **George.T.John**. There are 4 cases which had fever. Out of the 4 cases two patients had pneumonia, one had urinary tract infection and the last patient had retroperitoneal abscess. The organisms that were involved were Pseudomonas, Klebsiella, E.coli, and Enterobacter. All the organisms are basically hospital derived pathogens and they are no different from a normal person. All of them recovered from infections and survived the scare. We had one recurrence from the 4 cases, which is the retroperitoneal abscess. He is under treatment in the hospital for the same, now. Despite immunosuppression and in concurrence with traditional belief we never had any bizarre infection in this period. Urinary tract infections are the most common cause of fever in the study by **Ram et al**,

whereas pneumonia is the common organism in our study in this early group.

In the intermediate transplant period, the most common infections in our study were mucormycosis (13%) and polymicrobial infections (13%). The next common infections following the above were aspergillus and pneumococcus. Each of them contributed to 8.8% each. A majority of the percentage (26%), in this group did not have a diagnosis and fell in the undiagnosed category. Among the common sites, respiratory tract contributes to the majority followed by skin. Rest of the system mentioned previously more or less had equal involvement. Tuberculosis was noted just over 4%.We had only one case of CMV compared to 21% in **Ram et al** study and 16% of **Shakuja et al**[33]. One reason is,their studies are based on infection where as ours is based on fever and many CMV infected patients may have been diagnosed but not tabulated as they were not febrile.

In the late transplant period, urinary tract infections, respiratory tract infections and gastro intestinal infections are the common foci. Aspergillosis, Hepatitis C viremia and the undiagnosed category contributed to 45% and each contributing to 15%. Aspergillosis has adverse occurrence with prevalence of just over 10% in Indian literature[34]

and 0.7% in western literature[35]. Tuberculosis, Herpes, E.coli, polymicrobial infection account for 10% each. Percentage of tuberculosis varied between 3 to 13% in the Indian studies and in our study it is 4% in the intermediate group and 10% in the late infection group.

EARLY TRANSPLANT PERIOD	INTERMEDIATE TRANSPLANT PERIOD*	LATE TRANSPLANT PERIOD*
HOSPITAL ACQUIRED • E COLI • PSEUDOMONAS • KLEBSIELLA • ENTEROBACTER	• MUCOR • POLYMICROBIAL • PNEUMOCOCCUS • ASPERGILLUS • TUBERCULOSIS • PSEUDOMONAS • CRYPTOSPORIDIOSIS • HCV • ENTEROBACTER	• ASPERGILLUS • HEPATITIS C • TUBERCULOSIS • HERPES • POLYMICROBIAL • E COLI • KLEBSIELLA • CMV • BK VIRUS

TABLE 20: INFECTIONS DURING THE STUDY PERIOD IN OUR STUDY: CLASSIFIED AND TABULATED

Another important area of interest is polymicrobial infection, which in our study had significant impact on the patients. There were five cases of polymicrobial infections, three in the intermediate group and two in the late group. Well unfortunately, every patient with such infection in the intermediate group died.

A quick review of mortality yielded very important information. Nine out of the 45 patients expired in the study. It contributes to an alarmingly high 20%. But it is very low compared to the studies in tropical countries with mortality rate between 20% - 60%[12]. All of them are males. The most common site of infection is lung contributing to 66%. Most common organisms were Aspergillus and polymicrobial infections contributing to 27% each. All patients with aspergillus pneumonia (aspergillus involvement of other system not equally lethal in our study) and as mentioned earlier all polymicrobial infection in the intermediate group died.

We had 5 readmissions and four of them are admitted with infection of same organism. Two of them died.

Shortcomings of the study:

1. We had 3 attritions. They did not get followed up properly and were essentially excluded from the study.
2. Due to serious nature of the disease, few patients were started on empirical antibiotics prior to culture. This could have suppressed few of the organisms, which might have grown in the culture otherwise.
3. Culture for few fastidious organisms could not be done due to technical and financial constraints.
4. Few were diagnosed with corroborative evidence and marked improvement with treatment.
5. It under estimates the patients with infection because many infected patients were afebrile and cannot be included in the study.
6. Study population and study period is small to be compared with other national and international study.

CONCLUSION

We had studied renal transplant recipient patients, who had fever during the study period. We had patients who presented to us with infections but without fever. We never noticed any patient with non infectious cause of fever (or few of the undiagnosed could have been a non infectious cause). We had more men in the list and only men in the mortality list, which may be due to the significant number of males who underwent transplant. Other demographic data did not yield striking notifications. Most of them had live related donors and all of them were immunized properly, compliant with pneumocystis prophylaxis and immunosuppressed with prednisolone, tacrolimus, mycophenolate mofetil. Among the patient treated with rejection 57% had respiratory infections. One third of the patients had high tacrolimus values and 57% patients with high tacrolimus values had respiratory tract infections. Seven patients had NODAT in this study. Majority of the patients with fever had clinically no other clue to find the focus. Besides culture, CT chest proved to be the single cost effective tool.

Early infections were nosocomial and is similar to any post-operative patient. Among the intermediate group, common organisms were mucor and polymicrobial infections and the common site was lung.

In the late infections group urinary tract, respiratory tract, gastro intestinal tract were commonly involved and Aspergillus and Hepatitis C viremia were the common organisms.

Tuberculosis had a low incidence contrary to what we expected. Only one case of Cytomegalovirus was reported and no pneumocystis probably due to prophylaxis, in contrast to 15% in the study from NIMS[32]

Over all, a very satisfying experience to analyse the cause of fever in renal transplant recipients and to chart the common infections that is existing in our locality. Hope we think about the common infections and red flag information, which we analysed through the study, comes to our mind every single time we treat them. (After all, their life means much more to their family after transplant).

ANNEXURES

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PROFORMA

- NAME : SL. NO:
- AGE /SEX:

HISTORY

1. DONOR:

NATURE OF DONOR : (LIVE RELATED/DECEASED)

ANY KNOWN DISEASE/ COMORBIDITY IN THE PAST/EXISTING:

EPIDEMIOLOGICAL FACTORS/ EXPOSURE PRIOR TO TRANSPLANT:

2. RECIPIENT:

NATIVE KIDNEY DISEASE:

NATURE OF IMMUNOSUPPRESSION:

(RECEIVED INDUCTION: YES/NO)

TREATMENT FOR REJECTION, IF ANY:

POST OPERATIVE COMPLICATIONS, IF ANY:

APPROPRIATE VACCINATION:

COMPLIANCE ON PCP PROPHYLAXIS:

PRESENCE OF NODAT (New Onset Diabetes After Transplant):

LEVEL OF TACROLMUS

TIMING OF FEVER SINCE TRANSPLANT:

< 1 MONTH

1- 6 MONTHS

> 6 MONTHS

PATIENT'S FEVER DESCRIPTION:

SIMILAR ILLNESSES/ SIGNIFICANT ILNESSES IN BOTH PRE & POST TRANSPLANT PERIODS:

3. RELEVANT HISTORIES AS APPROPRIATE AS THE PATIENT'S SCENARIO DEMANDS

RELEVANT CLINICAL EXAMINATION:

INVESTIGATIONS (TAILORED FOR EACH CASE):

FINAL DIAGNOSIS:

FOLLOW UP (IF APPLICABLE):

MASTER CHART

S NO	NAME	AGE	SEX	PRE EXIST DISEASE	EPI EXPOSURE	NKD	NATURE OF DONOR	NATURE OF IMMUNOSUPPRESION	TREATMENT OF REJECTION	VACCINATION	PCP PROPHYLAXIS COMPLIANCE	LEVEL OF TACROLIMUS	NODAT	TIMING OF FEVER POST TRANSPLANT	PAST ILLNESS	RELEVANT CLINICAL DATA	CLINCHING INVESTIGATIONS	FINAL DIAGNOSIS	FOLLOW UP
1	nazer ali	27	m	nil	nil	nk	C	TI	yes	yes	compliant	HIGH	yes	>6 months	nil	no other clues	granuloma in bm biopsy	tuberculosis	fine
2	john	20	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	yes	>6 months	nil	no other clues	none	undiagnosed	fine
3	giri	23	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	>6 months	nil	abscess in ring finger	pcr for tb +	tuberculosis	fine
4	alli	45	f	nil	nil	nk	C	TI	no	yes	compliant	IN RANGE	no	1-6 months	nil	vesicles in dermatomal distribution	tzanck smear	herpes zoster	fine
5	shankar	53	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	1-6 months	nil	swelling L wrist	granuloma in synovial biopsy	tuberculosis	fine
6	kesavan	37	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	>6months	nil	no other clues	anti hcv and rna +	hepatitis	fine
7	amthul nali	29	f	nil	nil	nk	C	TI	no	yes	compliant	IN RANGE	no	>6months	nil	no other clues	pp 65 positive	cmv	fine
8	srinivasan	14	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	1-6 months	nil	cough;otherwise normal	ct chest and sputum culture - pneumococcus	pneumococcal pneumonia	fine
9	santhana kumar	14	m	nil	nil	nk	C	TI	no	yes	compliant	IN RANGE	no	>6months	nil	no other clues	nil	undiagnosed	fine
10	suresh	37	m	nil	nil	nk	L	TI	no	yes	compliant	HIGH	no	>6months	nil	cough	ct chest shows patch and sputum culture -ve	pneumonia and agent not known	fine
11	Raghu	40	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	>6months	nil	headache	csf- polymorphs	acute cns infection	death
12	karuppusamy	30	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	1-6 months	nil	nil	nil	undiagnosed	fine
13	dhanalaxmi	23	f	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	>6months	nil	ear discharge	urine c/s-klebsiella;ear discharge c/s-aspergillosis	uti and csom	fine
14	selvam	43	m	nil	nil	nk	L	TI	no	yes	compliant	HIGH	yes	1-6 months	nil	nil	nil	undiagnosed	fine
15	murugan	40	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	1- 6 months	nil	nil	smear for mp - +ve	malaria	fine
16	jayaprakash	28	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	yes	>6months	nil	vesicles in dermatomal distribution	tzanck smear + ve	herpes zoster	fine
17	srinivasan	14	m	nil	nil	nk	L	TI	no	yes	compliant	HIGH	no	<1 month	nil	post op	blood c/s- pseudomonas	pseudomanal-septicemia	fine
18	somasundaram	22	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	1-6 months	nil	vesicles	tzanck smear-+ve	varicella zoster	fine
19	shanmuga perumal	18	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	<1 month	nil	nil	urine c/s - e coli	uti	fine
20	devi	31	f	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	>6 months	recurrent uti	nil	urine c/s - e coli	uti	fine
21	mohammed rafi	24	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	>6 months	nil	cough	ct - pns- ?fungal ball; biopsy - aspergillosis	fungal sinusitis	fine
22	venkatesan	39	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	1-6 months	nil	nil	smear for mp - +ve	malaria	fine
23	poonkodi	45	f	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	>6 months	nil	vesicles in dermatomal distribution	tzanck smear-+ve	herpes zoster	fine
24	ramesh	25	m	nil	nil	nk	C	TI	no	yes	compliant	IN RANGE	yes	>6 months	nil	icterus	hcv rna significantly high	acute hepatitis hcv related	fine
25	manjunathan	22	m	nil	nil	nk	L	TI	yes	yes	compliant	IN RANGE	no	>6 months	nil	nil	hcv rna significantly high	hepatitis hcv related	fine
26	ranjith kumar	26	m	nil	nil	nk	C	TI	yes	yes	compliant	HIGH	no	<1 month	nil	crepitation over lung fields	ct chest- b/l pneumonia;culture - klebsiella	nosocomial peumonia	fine
27	devaki	23	f	nil	nil	nk	C	TI	no	yes	compliant	IN RANGE	yes	>6 months	nil	nil	nil	undiagnosed	fine
28	kumaresan	28	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	>6 months	recurrent uti	nil	uti;c/s- ecoli; decoy cells-	uti;e coli; bk virus infection	fine
29	antony	25	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	1-6 months	nil	fever;diarrhoea	nil	undiagnosed	fine
30	jeyaraj	35	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	1-6 months	nil	nil	nil	undiagnosed	fine
31	munuswamy	35	m	nil	nil	nk	L	TI	no	yes	compliant	HIGH	no	1-6 months	nil	nil	febrile neutropenia;consolidation in ct chest	pnemococcus pneumonia and sepsis	death

32	suresh	39	m	nil	nil	nk	L	TI	no	yes	compliant	IN RANGE	no	1-6 months	nil	nil	polymicrobial sepsis in blood culture	polymicrobial sepsis	death
33	ranjith kumar	23	m	nil	nil	nk	L	TI	yes	yes	compliant	HIGH	no	1-6 months	t op pneumo	cough	ct chest left lung abscess;pseudomonas and aspergillosis	lung abscess with sepsis	death
34	jerry bosco	48	m	nil	nil	nk	L	TI	yes	yes	compliant	HIGH	no	1-6 months	nil	nil	pneumonia in ct chest;sputum c/s-poly microbial	pneumonia with sepsis	death
35	govindaraj	43	m	nil	nil	anti gbm	L	TI	no	yes	compliant	IN RANGE	no	1-6 months	nil	nil	pneumonia in ct chest;sputum c/s-mucor	pneumonia with sepsis	death
36	prabhu	35	m	nil	nil	nk	L	TI	no	yes	compliant	HIGH	no	1-6 months	nil	cavernous breath sounds;	cavitating pneumonia;sputum-aspergillosis	pneumonia with sepsis	death
37	arasu	40	m	nil	nil	nk	C	TI	no	yes	compliant	HIGH	no	1-6 months	nil	fever;diarrhoea	nil	undiagnosed	death
38	poongodi	40	f	nil	nil	nk	C	TI	no	yes	compliant	IN RANGE	no	1-6 months	nil	icterus	hcv rna significantly high	hcv related hepatitis	fine
39	saravanan	39	m	nil	nil	nk	L	TI	yes	yes	compliant	HIGH	yes	>6 months	nil	cough	ct chest- pneumonia;c/s-aspergillosis	aspergillosis pneumonitis	death
40	kandaswamy	45	m	nil	nil	nk	C	TI	no	yes	compliant	HIGH	no	1-6 months	nil	nil	ct-chest-patch;FNAC-mucor	mucormycosis	fine
41	kandaswamy	45	m	nil	nil	nk	C	TI	no	yes	compliant	HIGH	no	>6 months	nil	nil	ct-chest-patch;FNAC-mucor	mucormycosis	In hospital
42	gopalakrishnan	26	m	nil	nil	nk	L	TI	no	yes	compliant	HIGH	no	<1 month	nil	abdominal pain;	ct abdomen pus collection;aspiration and culture-enterobacter	retroperitoneal abscess; enterobacter	fine
43	gopalakrishnan	26	m	nil	nil	nk	L	TI	no	yes	compliant	HIGH	no	1-6 months	retroperitoneal abscess	abdominal pain;	ct abdomen pus collection;aspiration and culture-enterobacter	retroperitoneal abscess;enterobacter ;recurrence	fine
44	arasu	40	m	nil	nil	nk	C	TI	no	yes	compliant	HIGH	no	1-6 months	nil	fever;diarrhoea	nil	undiagnosed	death
45	chinna ettu	25	m	nil	nil	nk	L	TI	yes	yes	compliant	IN RANGE	no	1-6 months	nil	diarrhoea	stool microscopy and acid fast-cryptosporidiosis	cryptosporidiosis	fine

KEY FOR MASTER CHART

M	Male
F	Female
NKD	Native Kidney Disease
NK	Not Known
L	Live Related
C	Cadaver
TI	Triple immunosuppression with prednisolone, tacrolimus, mycophenolate mofetil

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INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work	: Fever in Renal Transplant Recipients – An Inquiry into Etiology
Principal Investigator	: Dr. K. Jagdish
Designation	: PG in M.D (Gen.Med.)
Department	: Department of General Medicine Government Stanley Medical College, Chennai-1

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 06.03.2012 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு

சிறுநீரக மாற்று அறுவை சிகிச்சை செய்த நோயாளிகளுக்கு ஏற்படும் காய்ச்சலுக்கான காரணிகளை கண்டறியும் ஆய்வு

ஆராய்ச்சி நிலையம் : அரசு ஸ்டான்லி மருத்துவமனை
சென்னை - 600 001.

பங்கு பெறும் நோயாளியின் பெயர் : வயது:

பங்கு பெறும் நோயாளியின் எண் : பாலினம்: ஆண் ☐ பெண் ☐

நோயாளியின் விலாசம் :

நோயாளி இதனை (√) குறிக்கவும்.

மேலே குறிப்பிடப்பட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும். அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் என்னை இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்க அனுமதிக்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் என்னை இவ்வாய்வில் இருந்து விலக்கி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். என்னை ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் என்னை ஈடுபடுத்த முழுமனதுடன் ஒப்புக் கொள்கிறேன். ☐

நோயாளியின் கையொப்பம்..... இடம் ..... தேதி.....

கட்டைவில் ரேகை (இந்த படிவம் படித்து காட்டப்பட்டு புரிந்து கைரேகை அளிக்கின்றேன்)

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி.....

ஆய்வாளரின் பெயர் .....